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Circulatory System Devices Panel

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P R O C E E D I N G S [8:15 a.m.]

Agenda Item: Call to Order

DR. CURTIS: I would like to call this meeting of the Circulatory System Devices Panel to order.

The first order of business will be the reading of the conflict of interest statement.

Agenda Item: Conflict of Interest Statement

DR. STUHLMULLER: The following announcement to address the conflict of interest issues is made to preclude even the appearance of impropriety and to determine if any conflict exists. The Agency reviewed the conflict states reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest. However, the Agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

For participation in today's discussion, all the panelists have been granted limited waivers of their employment of their employment or their financial interest in firms that could potentially be affected by the panel's decision. This includes Drs. Curtis, Gilliam, Sethi, Simmons, Brinker, Domanski, Perler, Ferguson, Hopkins,

Tracy, Reller, Danner and Ms. Whelan.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. CURTIS: Thank you.

What I would like to do first, as we get started, is have us all introduce ourselves. I am Anne Curtis. I am the chair of the panel and a cardiologist/electrophysiologist at the University of Florida.

DR. STUHLMULLER: I am John Stuhlmuller. I am a cardiologist with FDA and executive secretary for the panel.

DR. HOPKINS: Richard Hopkins. I am a cardiac surgeon, chief of cardiothoracic surgery at Brown University.

DR. BRINKER: Jeff Brinker, director of interventional cardiology and cardiac pacing, Johns Hopkins University.

DR. FERGUSON: Tom Ferguson, cardiac surgeon, Washington University School of Medicine, St. Louis.

DR. GILLIAM: Roosevelt Gilliam, electrophysiology in private practice in Richmond, Virginia.

MS. WHELAN: Social worker with HIV-infected adult population at St. Vincent's Hospital in Manhattan.

MR. JARVIS: Gary Jarvis, industry representative, panel, St. Jude Medical.

DR. CALLAHAN: Tom Callahan , director of cardiovascular respiratory neurology, FDA.

DR. RELLER: Barth Reller, Duke University, director of clinical microbiology and infectious diseases physician.

DR. DOMANSKI: I am Mike Domanski. I am a cardiologist and I head the Clinical Trials Group at the National Heart, Lung and Blood Institute.

DR. SETHI: Gulshan Sethi, University of Arizona, Tucson.

DR. SIMMONS: Tony Simmons. I am a cardiologist/electrophysiologist at Lake Forest University.

DR. TRACY: Cindy Tracy. I am the director of the Arrhythmia Service at Georgetown.

DR. DANNER: Robert Danner, I am head of the Infectious Diseases Section of the Clinical Care Medicine Department at NIH.

DR. CURTIS: The next topic will be opening remarks by Dr. Susan Alpert from the FDA.

DR. ALPERT: Thank you, Dr. Curtis.

Good morning. I would like to first thank all of you for attending today to discuss this very important issue and it is an issue that is very close to my heart. I am a microbiologist and infectious disease clinician, as well as director of the Office of Device Evaluation and I don't often get the opportunity to have all of my issues come together at the same time at a panel meeting, but today I have that opportunity.

The FDA is being approached by a number of manufacturers, who would like to add anti-infectives to their implantable cardiovascular products, most particularly heart valve convascular(?) grafts, but there are others as well. They tell us that today the surgeons are bathing, dipping or otherwise exposing grafts to solutions of anti-infectives prior to implantation in an attempt to prevent early infection.

The manufacturers are looking for guidance from the FDA as to how they might develop the information that would support marketing of coated or impregnated products to

meet this perceived need. So, they are looking for guidance from us on what kinds of studies, what kinds of data do they need to reasonably establish safety and effectiveness for this type of product.

We are worried. There is a great concern that anti-infectives are already being overused in many settings with the results of the development of resistance for many organisms and, therefore, decreased in the effectiveness of therapy with those or related drugs.

The rates of infection following implantation of heart valves and grafts, to the best of our knowledge, is low and to establish in the clinic that there is a benefit from coding such grafts, that this type of prophylaxis actually works, would require very large studies due to the low incidence of infection.

To address the risks and the concerns about increasing resistance among infecting organisms and its impact on later treatment would also be a long and very large study. We have invited you today, all of the affected communities, to begin a dialogue with us to help us to develop the guidance that we are going to need to provide to industry in this area.

We need to hear from the manufacturers themselves regarding their concerns about conducting such studies. What do they propose as an appropriate mechanism to develop

necessary data to support reasonable safety and effectiveness of antimicrobial coated or cardiovascular devices, what problems do they foresee in conducting such trials.

We need input from the cardiovascular clinical community regarding the patients' needs and the infection risks posed by such devices and procedures. Specifically, are there subsets of patients in whom the risks of infection are sufficiently great that it would be appropriate to study coated devices, impregnated devices in such patients?

Are the benefits and the risks in the right balance to move those types of studies forward? We need input from the infectious disease community regarding potential antimicrobial choices and the risks of resistance as a result of such practices.

What questions should we be asking about specific drugs that manufacturers' sponsors are desiring to incorporate into their devices? What are the preclinical studies that need to be done? Is there animal work that should be done to precede the clinical?

How should we design studies to address the concerns of emerging resistance? There are many questions, such as these, to be answered. And we don't expect that today's discussion will give us a final answer on them. This is really the initiation of what we hope will be a very

productive dialogue.

We also recognize that the issue is not limited to cardiovascular devices or for grafts and heart valves alone. But we needed to begin somewhere. We believe that the benefits and risks may be great in this community and, therefore, have chosen to begin the dialogue in this particular area.

Again, let me thank all of you, panel members and participants from the audience, for coming today. In particular, I want to thank our colleagues from the Anti-Infective Drug Panel and from the NIH for joining us for this important discussion.

What we are looking for is guidance on the issues, some input from you as to how we ought to begin to develop this process and we can guarantee that we will be back to you as we move forward and develop either points to consider a guidance. We will be back to discuss it with you.

Again, thank you very much.

DR. CURTIS: Thank you.

Agenda Item: Open Public Hearing

We will move on now to the open public hearing. We have two speakers, who have requested time. As each speaker comes to the podium, please identify yourself and identify any financial interest you may have with any companies or the subjects being discussed today.

The first speaker is Dr. James Anderson.

DR. ANDERSON: Good morning. Thank yo for the opportunity to talk.

My name is Jim Anderson. I am a professor of pathology, polymer science and biomedical engineering at Case Western Reserve University.

DR. CURTIS: Do you have any financial interest?

DR. ANDERSON: I have been a consultant for most of the major heart valve and vascular graft companies over the years. However, today, I am here on my own. I am representing basically myself and what I feel is a significant problem that I have been involved in, I would say, for the last 20 years. And I will speak a little bit more about that a little later.

My goal today is to acquaint you with the pathology of prosthetic valve endocarditis and also other vascular types of infections. While we do discuss the issue of infection and the treatment with antibiotic, we have to appreciate the debilitating effect that non-treatment with these vascular devices leads to.

I would like to begin with showing you the pathology and what the current thinking is on the pathophysiology of devices. As a pathologist, who has been doing implant retrieval since 1979 and has probably looked at over 7,000 clinical cases of devices, it is quite common

to see infections.

Here is an example of an expanded tetrafluorethylene vascular graft with an infectious process. Now, this was used in a hemodialysis patient and you can appreciate the combination there of the thrombus, as well as the infectious nidus. And you will notice the fibrin cap. This is an important part of the pathophysiology because it is postulated that antibiotics diffuse slowly through that fibrin cap and that these bacterial colonies continue to proliferate and any sort of systemic antibiotics is limited in controlling these infections.

The next slide shows a close-up of that. For the last 20 years, I have been interested in what I call controlled release devices, although I guess a better, perhaps more broader term would be anti-infectives and a coating on a vascular graph like this might combat the propensity for having an infection like this.

Any infected device has to be considered for removal and there is a certain morbidity and sometimes a mortality involved in the removal of these types of devices. Here we see another cardiovascular type of device, the temporary pacemaker that is put in the right ventricle. This was a diagnosis that I made at autopsy. This was never diagnosed in the patient.

And subsequent work up of that apparent thrombus on the pacemaker lead showed a candida infection. This was an immunocompromised patient. This points out the occult or silent nature of these infections. By the time intervention is made, it is usually too late.

Here, this is a bioprosthetic heart valve removed from a 14 year old boy, who had a pacemaker pocket infection. And there we see the residual of the infection, which is a calcification that has fused the two cusps of the valve and although the valve itself, it is unclear as to whether it was infected or not, it at least had a focus of infection that led to subsequent valve dysfunction and resulted in the removal of that heart valve.

Another example is, again, a bioprosthetic heart valve diagnosed at autopsy. This was occult. It was silent. It was never diagnosed. And there you can see on the left hand side of the screen in the annulus within the myocardium an abscess pocket, which had formed. There is the closeup of the histology and you can appreciate the micro abscesses that can result in a silent nature in these patients.

This is important because when the surgeon goes in to remove this, he must debride the annular tissue until he has viable tissue in which he can suture the new heart valve into place. Many times this involves insertion of an

annular ring, which in itself can lead to flow disturbances and dysfunction of the heart valve and subsequent morbidity.

There we see another example of an infection and this is an abscess. This was the size of my thumb when I removed this or when I discovered this at autopsy. This, again, was an occult case. This is another view of that.

So, I think the first thing we have to consider when we deal with infections of cardiovascular devices is the silent or occult nature of these. They don't normally present until we do the autopsy, if we do the autopsy.

So, sometimes the incidence and the numbers involved, perhaps, are misleading. In many cases, we don't do autopsies on these patients. So, we don't have a clear idea of the incident.

Now, this case here shows what can happen with prosthetic valve endocarditis, that the rig, the sewing ring itself, becomes infected, that there is infiltration or penetration into the endocardial cushion or the annulus and this then can extend into the myocardium, leading to myocardial abscesses.

Several studies have showed that in fatal prosthetic valve endocarditis that annular invasion can be as high as 85 percent and that myocardial abscess formation can be as high as 50 percent. So, although the incidence of diagnosed infection is low, the complications are most

serious.

Extension from the myocardial abscess can go into the pericardium leading to pericarditis and this then itself can lead to conduction system dysfunction, which may be the ultimate cause of death in some of these patients. I have described the -- and you can see very well the issue of the necrotic annulus and the need to debride, but on the other hand this is not always done and suture pull out occurs from the necrotic annular tissue leading perivalvular leaks.

Finally, with debridement, we have to consider the issue of moving closer and closer to the conduction system when we do suture in the new valve and it is documented in the literature that sutures utilized in the fixation of valves have penetrated the conduction system leading to conduction system disturbances and death.

So, in 1979, Dick Jones, Larry Olinoff(?) and myself developed a prosthetic heart valve that had a gentamicin-releasing insert within it. And we actually did dog studies on it. We did pharmacokinetic studies on the gentamicin and the systemic levels in the blood stream with gentamicin.

So, this concept is not necessarily new, but I think we know more than we think we know about how to investigate these types of devices and I certainly -- as a pathologist, I think that they have a place in the

armamentarium for treating patients while we still have the opportunity to treat them and not define these types of occult or silent infections at the autopsy table.

One thing I did not talk about was my -- well, I guess I did mention my financial interests, but I would like to reiterate that I am here in a sense representing at least what I see as a pathologist and my longstanding interest in medical devices and, frankly, the care of people who need medical devices.

Thank you.

DR. CURTIS: The next speaker will be Dr. Darouiche.

DR. DAROUICHE: Good morning.

I would like to thank you the FDA for taking the initiative to assemble this distinguished panel of experts and for allowing me to speak to you today. My name is Rabih Darouiche. I am an infectious disease physician at Baylor College of Medicine and the Houston VA Medical Center.

I am a clinician, who takes care of patients with prosthetic valve endocarditis and infections associated with vascular grafts and catheters. I am also a researchers, who has served as a principal investigator for a number of prospective randomized multi-center clinical trials that have examined the efficacy of antimicrobial coated catheters.

In addition, I have served as a consultant for infection control measures for Sulzer Carbomedics, Inc., which is a heart valve manufacturing company. However, today, I have paid all of the expenses associated with my trip today. So, I am here today on a personal level, essentially to speak to you about three topics, which are why should vascular device-related infections be prevented and how.

Second, I would like to comment briefly on the established role of antimicrobial coated central venous catheters. And, lastly, I would like to comment on the potential impact of antimicrobial coated prosthetic heart valve on the prevalence on antibiotic resistance.

To start with the first objective, Dr. Anderson has beautifully outlined the reasons we are all concerned about prosthetic valve endocarditis linked to the fetus morbidity due to the local infection, extra cardiac complication, as well as the high mortality ranging from 21 percent to 43 percent.

Now, what have we learned from our previous experience with antimicrobial coated central venous catheters, which are another part of vascular devices? In two back-to-back articles published in the August issue of the Annals of Internal Medicine last year, there were two articles that reported the efficacy of antimicrobial coated

central venous catheters and preventing catheter colonization and catheter latent blood stream infection.

This work was so important that it had to be followed by an editorial by the CDC, highlighting this new strategy for prevention of device-related infection. Please remember that these are the only two types of antimicrobial coated central venous catheters that have ever been shown in prospective randomized clinical trials to reduce rates of catheter colonization and catheter latent blood stream infection.

The first one was coated with antiseptic combination of chlorhexidine and silver sulfadiazine. And the second one was coated with the antibiotic combination of minocycline and rifampin. The first report showed that catheters coated with chlorhexidine and silver sulfadiazine were twofold less likely to be colonized and about fourfold less likely to have catheter latent blood stream infection when compared with uncoated catheters.

In the second study of minocycline and rifampin coated catheters there was a threefold reduction rate of catheter colonization and essentially there was a complete eradication of catheter latent blood stream infection. Now, does the medical literature refer to these agents as antibiotics versus antiseptics? From a clinical perspective, to us as clinicians, we understand antibiotics

as those drugs that can be administered systemically or locally to treat infection.

However, they may also be administered systemically or locally to prevent infection. In contrast, antiseptics are generally applied locally to prevent infection but not to treat infection. It is important, though, to distinguish between different classes of antibiotics. There are those that are considered antibiotics of choice for treatment of certain infections, particularly vancomycin, which is the only drug available in the United States for treatment of methicillin-resistant staphylococcal infection.

In contrast there are a group of other antibiotics that we refer to in the medical community as alternative antibiotics that are used occasionally to threat infection if patient is allergic or intolerant of antibiotics of choice.

Now, the findings from these two clinical trials indicated that, in fact, antimicrobial coated central venous catheters be coated with antiseptics or alternative antibiotics were unlikely to cause immersions for antibiotic resistance. When organisms were recovered from antiseptic coated catheters, antibiotic coated catheters, as well as uncoated catheters, the antimicrobial susceptibilities were essentially the same. So, as coated catheters become

colonized with bacteria, it is generally not because of resistant bacteria. It is because there is not a single system that is completely perfect and in certain situations bacteria may overwhelm the protective efficacy of coated catheters.

That is well anticipated because, in fact, there are scientific reasons as to why, for example, antibiotics -- catheters coated with alternative antibiotics, such as minocycline and rifampin, are unlikely to cause antibiotic resistance, first, the synergistic activity of this combination. Second, these two drugs have different mechanisms of action, so it is unlikely for bacteria to develop concomitant resistance to two antibiotics with two different mechanisms of action. Third, there is a very low ratio of bacteria at antibiotic levels on the catheter surface, which does not favor resistance, as compared with atrophies, where the opposite is true.

Both agents are lipophilic. They leach proportionately off the catheter surface. There is no danger that one antibiotic may remain on the surface while another may leach off completely and most importantly there are no detectible systemic antibiotic levels.

Now, what have we learned from these two studies? These two protective catheters showed three similarities. First, neither is coated by antibiotic of choice for

treatment of established infection. So, neither is using vancomycin.

Second, each catheter is coated with a combination of antimicrobial agents. The use of a combination of agents for coating does help prevent antimicrobial resistance and, in fact, provides a broad spectrum antimicrobial activity that would help prevent supra infection or vancomycin where only gram parts of coverage is provided with these combinations we can make sure that supra infection by gram negative bacteria and candida does not occur and, thirdly, each catheter provides its own inhibition as you see in this damage over here due to the controlled, slow leaching of the agents off the surface of the device.

How can we apply this knowledge to deep cardiovascular implants? At the present time, antibiotics are used to prevent prosthetic heart valve endocarditis in one of three fashions or can be used in one of three fashions. Are there perioperative systemic antibiotic prophylaxis for dipping prosthetic heart valves in antibiotic solution before implantation or coating prosthetic heart valves sewing cuff with antibiotics.

The first option of perioperative systemic antibiotic prophylaxis, the fact of the matter is that although this constitutes a standard of care. This approach was never scientifically proven to be protective. In fact,

the only study that has looked at this approach in preventing prosthetic valve endocarditis was published by Goodman back in The New England Journal of Medicine, 1968, where he actually abandoned the placebo arm of a prospective trial of antimicrobial prophylaxis in prosthetic valve surgery, when endocarditis developed in two placebo recipients.

So, we continue to use the standard, although it has never been scientifically to be protective, but we think it is. Now, despite the lack of convincing clinical data supporting superior protection by vancomycin versus cephalosporin, a number of hospitals, including mine, have actually started using systemic vancomycin for prophylaxis, which is associated with an increased likelihood of antibiotic resistance.

The second option of dipping devices in antibiotics before implantation, the only study I could find was a study published in the Italian literature back in 1992, by Datu(?), et al. He compared the rates of endocarditis in 1,226 patients, who had the devices dipped in antibiotic solution before implantation and compared them with patients with untreated devices. The overall incidence of endocarditis was at least what fourfold less likely in those who received treated versus untreated devices, but what is even more important is that the differences were

very much magnified in prevention of early endocarditis.

The last approach of coating sewing cuffs of antibiotics in vitro in animal studies have already showed that these sewing cuffs inhibit bacterial colonization. They do provide controlled leaching of antibiotics from coated devices to produce effective zones of inhibition that help inhibit bacterial adherence not only to the surface of the device but as we have seen with antimicrobial coated central venous catheters, it is very important to inhibit bacterial growth within the biofilm around the device.

However, because of the time consuming and the number of patients needed, understandably, no clinical trials have been done. How do we compare local use of antibiotics for prevention of endocarditis, if you use a coated device as opposed to dipping the device in antibiotics before implantation, there are three advantages.

The first one is assure that antibiotics of choice for treatment of established infection that is vancomycin are not excessively used for prevention of infection. I just provided a letter to Dr. Stuhlmuller from the chief of surgery in our hospital. He implanted a total of 297 devices over the last 12 years.

Every single device was dipped in vancomycin. Rates of early endocarditis were zero. Rates of antibiotic resistance to vancomycin are sky high.

Second advantage, it provides control of amount of antibiotics bound to the device and the rate of release of antibiotics from the implanted device and, therefore, those pre-coated devices will adhere to the guidelines set by the FDA.

And, third, it does help infection control surveys in different medical centers so that we compare oranges with oranges and apples with apples.

And I would like to conclude by saying that antimicrobial coated heart valve will probably achieve all of these three objectives. It can improve patient care by reducing device colonization, which is a prelude to clinical infection. It does decrease overall cost of health care because it is a very cost saving measure and, in fact, if anything, it can enhance infection control because, in fact, if you use an antimicrobial coated heart valve that you know is going to be protective, the surgeon or the clinician is less likely to prescribe vancomycin in febrile patients with prosthetic heart valve for suspected or documented prosthetic heart valve endocarditis and by decreasing the use of vancomycin, we can all help in decreasing the rates of resistance to vancomycin.

Second, these devices have been shown to reduce the bacterial concentration in the biofilm and we know that it is bacteria in the biofilm that generally are likely to

be tolerant or resistant to bacteria. So, the use of this approach, hopefully, can reduce the likelihood of emergence of antibiotic resistance.

Thank you for your attention.

DR. CURTIS: We have a couple of letters that are going to be read into the record now.

DR. STUHLMULLER: The first letter is from Robert B. Wallace, M.D., of McLean, Virginia. In his letter Dr. Wallace indicates that he is a medical adviser for Sulzer Carbomedics and he was unable to attend the meeting today. He indicated this is an important topic for the panel to consider and that surgeons have used systemic antibiotics prophylactically with a beneficial effect and it is also the clinical practice of people to either apply topical antibiotics to the surgical field or rinse the valves with antibiotics.

He feels that the concept of coating the valve with antibiotics may be effective in preventing bacterial implantation on sewing rings during the perioperative period and reduce the early incidence of endocarditis.

The second letter is from James W. Jones from the Baylor College of Medicine and Veterans Affairs Medical Center in Houston, Texas.

Dr. Jones indicates that he has been immersing heart valve in Vancomycin solution for over 20 years and he

considers this to be a beneficial practice and that he has maintained records on 297 patients since 1986 and he has had no documented cases of early prosthetic valve endocarditis.

DR. CURTIS: Are there any other members of the public, who wanted to speak, before we move on to the industry presentations?

[There was no response.]

Agenda Item: Industry Presentations

Okay. If not, then we will move on to that and we will have a representative from the Health Industry Manufacturers Association step forward.

DR. BENSON: Good morning. I am Jim Benson, executive vice president of the Health Industry Manufacturers Association. HIMA is the largest medical technology association in the world and represents more than 800 manufacturers of medical devices, diagnostic products and medical information systems.

I appreciate this opportunity to discuss an important issue; that is, FDA's evaluation of antimicrobial coatings on permanent cardiovascular implants, including heart valves and vascular grafts.

I see today's panel as the first step in a series of open discussions among the industry, the agency and the clinical community and I congratulate FDA and, in particular, this panel, for taking that step. HIMA believes

that collaboration is the most effective way to develop policy based on a sound scientific footing.

I would hope those assembled here today view this as an opportunity to collaborate on an issue that needs to be considered from a scientific rationale.

This constructive dialogue actually started in late April when the Society of Biomaterials and the Surfaces in Biomaterials Foundation sponsored the Designer Surfaces on Biomaterials: A Regulatory Case Study Workshop. Representatives from FDA, the device industry and the medical and scientific community attended and participated. In fact, FDA, as co-chair, played a significant role in the conference.

Those present discussed clinical requirements for a hypothetical gentamicin coated heart valve cuff. During the discussion, it was proposed that a 3,000 patient randomized clinical trial would be required for a coating cuff having a therapeutic or prophylactic purpose. This would be a daunting requirement.

Such a preapproval requirement would diminish the incentive for a sponsor to pursue the development of potentially salutary coatings on heart valves and other cardiovascular implants. I fail to see how such an outcome would serve the public health.

Clearly, there is a visible need in the medical

community for antimicrobial coated implants. Today, for example, as you have just heard, some cardiovascular surgeons dip heart valves and vascular grafts into antibiotics prior to implantation.

These physicians are dipping devices to preserve them from microbial colonization. Unquestionably, this is done in their patients' best interest. Protecting the implant from pathogens stemming from the surgical procedure during the perioperative period enhances the likelihood that the device will not become contaminated. Avoiding the contamination attributable to the surgical procedure avoids the possible removal of an implant.

Importantly, to the extent the judgment of many cardiovascular surgeons is correct that dipping heart valves and grafts is beneficial, requiring a 3,000 patient premarket approval study would deny them of a similarly treated device produced under the strict quality controls required by the quality systems regulation. This is an unacceptable result. We need careful thought and consideration to achieve the appropriate public health outcome.

As FDA's former acting commissioner and director of the Center for Devices and Radiological Health, I was often confronted with significant public health and regulatory issues. Our challenge in this complex regulatory

arena was to protect patients from unsafe or ineffective devices while ensuring that beneficial devices still reached them as soon as possible.

In other words, consumers are best served when an appropriate level of regulation is achieved. While over-regulation may prohibit the marketing of unsafe and ineffective devices, often it deprives consumers of technologically advanced products.

Last November, Congress passed and the President signed into law the Food and Drug Administration Modernization Act of 1997. This law embodies this balanced approach to consumer protection. The law requires FDA to consider the least burdensome means necessary to establish device effectiveness.

Also, to facilitate reasonable premarket reviews and to facilitate prompt approvals, the new law requires FDA to consider the extent to which traditional premarket requirements could be addressed through less onerous postmarket controls. The new law's requirements counsel a responsible yet flexible approach to ensuring that patients will receive beneficial devices in a timely manner.

As a result, it is critical that blanket approaches not be taken. First, the manufacturer's proposed use for an antimicrobial coated implant must define the Agency's considerations such that appropriate scientific

review is a function of the claims made for the product.

The new law requires this result. For example, proposed labeling that states a device will provide a therapeutic effect should raise different substantiation considerations from labeling containing a device preservative claim.

The former is intended to treat a disease or condition, the later to preserve a device. Likewise, device labeling claiming a chronic effect should be understood differently than labeling claiming an acute or short term effect.

For example, a claim that an antimicrobial implant is intended to prevent patient infection for the implant's life is very different from an antimicrobial preservation claim limited to the perioperative period. The above set of claims raise different effectiveness and safety issues and, therefore, I urge you to consider recommending very different forms of substantiation.

Another important consideration for you to make relates to a coated device's design. For example, if alternative antimicrobial agents are used for coatings to protect an implant, instead of antibiotics of choice for treatment of established infections, you should consider whether the risk/benefit analysis would differ, assuming both are effective for their claimed purpose. Likewise, if

a combination of antimicrobial agents is used to coat an implant, how does this design affect the Agency's safety and effectiveness assessment of a coated device?

HIMA members understand the concern about creating resistant organisms, but believe that relying on alternative antimicrobial agents minimizes the risk of antibiotic resistance. Also, HIM members believe that certain antimicrobial combinations can reduce the likelihood of creating resistant organisms.

Importantly, limited, short term exposure to an antimicrobial coated device presents a very different situation from long term chronic exposures. Considerations of the type of drugs, how they are incorporated into a device and the nature of the antimicrobial exposure all raise issues for you to consider.

On the effectiveness side, the issue is just as stark. Today, when infection rates associated with heart valve and vascular graft surgery are low, in large part due to the pervasive use of perioperative antibiotics, is it necessary to require a huge preapproval clinical study on an antimicrobial coating's effectiveness when the local effect of the coating can be reasonably demonstrated with in vitro testing and in vivo studies in suitable animal studies?

Can certain post-approval controls compensate for a preapproval clinical study that may require innovation?

Your ingenuity in recommending pathways to solutions for these difficult issues is necessary and important. The question remains: Do consumers need a 3,000 patient trial to resolve the effectiveness issue?

In closing, we believe the public health will benefit from a balanced regulatory approach to antimicrobial coatings, one that weighs risks and benefits to determine what pre and postapproval requirements are needed to provide reasonable assurance of device safety and effectiveness.

Congress required FDA to rely on the least burdensome form of valid scientific evidence to clear devices for marketing in order to avoid delaying or effectively prohibiting the availability of potentially beneficial devices.

This is the form of consumer protection Congress and the President endorsed last November and it is the form of consumer protection I sought during my years at FDA.

To this end, I propose that the FDA, industry and the interested members of the scientific and medical community work together on this issue. We believe that our common knowledge represents the greatest opportunity for a successful public health determination about the use of antimicrobial coatings on permanently implanted devices.

Let me just add, I think this session is a good start at that collaboration. Thank you.

DR. CURTIS: A representative from Sulzer Carbomedics.

MR. MORTON: Good morning, Madame Chairperson. I would like to thank the Food and Drug Administration for bringing this question regarding anti-infective coatings before the advisory panel and I would like to thank the members of the panel for taking the time to consider this important topic.

My name is Michael Morton and I am the manager for U.S. Regulatory Affairs at Sulzer Carbomedics. I am employee of Sulzer Carbomedics. Today, I have also asked Dr. David Naftel from the University of Alabama-Birmingham to comment on considerations for clinical studies related to anti-infective coatings. Dr. Naftal is a consulting biostatistician for Sulzer Carbomedics.

Joining me also are representatives of our Research and Development and Clinical Affairs Departments from Sulzer Carbomedics, should there be any questions later on today.

Dr. Robert Wallace, our Carbomedics' medical advisor, was unable to join us today. He did send a letter to Dr. Stuhlmuller, which Dr. Stuhlmuller read. In that letter, Dr. Wallace said anything that may reduce the occurrence of early valve infection with its usual devastating results is important.

Sulzer Carbomedics agrees with Dr. Wallace and with other clinicians, who believe that there is a need for anti-infective heart valve cuff. And today, I would like to propose a model for discussion. A similar model was presently at the Regulatory Workshop, which was sponsored by the Society of Biomaterials and Surfaces for Biomaterials Foundation and the FDA also did participate in that. And we appreciate their participation.

This proposed model would be a modified device consisting of aortic and mitral models of the Carbomedics, known as the CPHV. The CPHV is currently approved for use in the United States. The CPHV would include a sewing cuff that is preserved by impregnation with an approved antibiotic or a pairing of approved antibiotics.

The antibiotic selected would be one that is not commonly used for a first line of defense against infection in cardiovascular surgery. The manufacturer would label the device as having a cuff preserved with the named antibiotic.

The manufacturer would not claim that efficacy had been determined in human clinical trials. The manufacturer would cite in vitro studies that demonstrate the existence of a zone of inhibition and in vivo studies, specifically small animal studies that would further demonstrate efficacy of the preserved polyester.

Sulzer Carbomedics would demonstrate safety

through in vitro testing and in large animal studies based upon appropriate tests taken from the DCRND Heart Valve Guidance Document.

Sulzer Carbomedics believes that because the proposed modification is the preservation of the sewing cuff of an approved heart valve, using an approved antibiotic and because safety can be demonstrated in vitro and in large animals and that efficacy can be demonstrated in vitro and in small animals, that further valid scientific evidence would not be needed to prove the safety and efficacy of such an anti-infective heart valve.

We are concerned that if premarket clinical studies are required of this valve, the number of patients will be large and the cost and the time required to conduct the clinical study would effectively prevent such a valve from reaching the patient.

Now, I would like to ask Dr. Naftel to provide his thoughts regarding clinical studies for such an anti-infective heart valve.

Dr. Naftel.

DR. NAFTEL: My name is David Naftel. I am a statistician in the Department of Surgery at the University of Alabama in Birmingham. I have been working with heart valves for about the past 15 years.

As Mike said, I am a consultant to Sulzer

Carbomedics and I appreciate this opportunity to speak.

In 1994, the FDA Heart Valve Guidance Document created the -- first proposed the Objective Performance Criteria. This was quite a landmark in the development of new valves because it gave us a standard or standards and gave something to compare against.

The OPCs were expected to be used for all new valves to demonstrate safety. The general idea is that a premarket study must demonstrate that a new valve has a morbid event rate that is less than twice the OPC. Based on this ruler and this way of thinking, Gary Gruncamyer(?), Diane McCullock Johnson and I wrote a paper and worked with the FDA to calculate sample sizes necessary for new valve studies. This was done in terms of years.

At that time, we calculated that it would be necessary to have a study for a new valve that contained at least 800 valve years, years of exposures for patients, to prove that your new valve was less than twice an OPC of 1.2. 1.2 was the focused and it is interesting that that is the one that is for endocarditis.

I should also say that looking through the literature and really looking at everything I could find, I believe that this rate that FDA came up with is a good rate. Certainly, it is not constant through the years, though. It peaks in the first few months and becomes quite small after

about six months.

So, this gave us a baseline to look at safety to prove that a valve was better than twice the OPC. Now, in order to approve efficacy, though, things change. Now we must prove superiority and I believe there are two ways that this could possibly go, both of which will produce very large numbers. One is by OPC comparisons, again, and here is a table I put together. If you assume an OPC of 1.2 percent and if you want to show that a new valve or a new coating gives a rate that is half of that, I calculated that it would actually take 4,860 valve years or if you had a study where each patient had an average of three years, that would be 1,620 patients; a very large study to say the least. And this is to compare against the constant.

I actually think it would be scientifically more appropriate in this case to have a randomized trial. And in that case, I put together this table where if you were comparing two valves or a valve with a coding and without and if you looked at the expected rate of 1.2 percent, say, in the first year and if you were hoping to decrease that to .8 percent, it would take 10,000 patients in each group or if you thought that the new version produced a rate that was half of the standard of 1.2, that would take 4,000 patients in each group.

So, as has already been said several times this

morning and I am sure we will say again and again, it would take an incredibly large study to prove efficacy.

So, there are four points from these large numbers. First of all, any good statistician can come up with any good number -- actually, a bad statistician can do that also -- so, you can play this game, and I hate to even put those words together, any way you want, but the fact is that the numbers will be very large.

Obviously, then, this would be costly and very lengthy and what impressed me most is it would require -- to prove efficacy would require a study that is much, much larger than the required study for a brand new valve starting from scratch. So, that was a point that was impressive and a little bit sobering to me.

Now, I don't know if it is appropriate, but if anyone had any questions, I would be glad to try to answer them at this time.

That ends our formal presentation. We will be standing by to answer any questions.

Thank you.

DR. CURTIS: All right. Thank you.

Agenda Item: Open Committee Discussion

We are going to be moving on to the panel discussion now. It is a little bit different from some of the other ones we have done.

We were given a set of questions and they were revised slightly and they were put in front of each of the panel members this morning, if you could refer to that.

I think the best way to handle this may be to go through each question and then have a general discussion about each of the issues. I wanted to ask first if there were any of the panel members, who wanted to make some opening remarks about this subject. I think we are going to depend a lot on our infectious disease experts today to give us some guidance on this.

I think what I will do is we will use the questions as a framework for discussion and certainly as we go along, if there are questions or issues that we need addressed, we can ask some of the people who have spoken already and get some clarification on things.

In terms of the questions posed to us, the first one that we were given is: Are there particular types of cardiovascular implants where the risk of infection warrants such strategies, meaning the antimicrobial coatings? How should this potential benefit be evaluated in light of the risk of the development of antibiotic resistant organisms for the patient and for the community?

DR. SETHI: I think this is a very important issue. Those of us who use these devices or implanted devices, feel that -- at least I feel that the complication

of infection is disastrous to the patient. The outcomes are very bad. And anything we can do to improve it is worthwhile.

We all have used the mechanical valves and antibiotics, hoping we are reducing the infection rate. I am not sure in my mind whether we do or not. So, anything we can do to learn that we are doing something good is worthwhile.

DR. CURTIS: Let me ask the surgeons on the panel, how widespread is the practice of dipping valves in antibiotic solutions? Is it common? Do most surgeons do that? Is it very idiosyncratic and only done occasionally?

DR. HOPKINS: It is idiosyncratic but I think it is very common, either dipping or spraying the cuff with one antibiotic or another. Some surgeons use antibiotics, which are commonly used, like gentamicin. Others, myself included, try to use antibiotics that are rarely used, thinks like bacitracin or that kind of -- kanamycin -- things that are rarely used intravenously. But it is a common practice.

DR. SETHI: I think more common than implanting the valve in the endocarditis patients. In the routine patients we may not do that. In a patient with a native(?) valve endocarditis or with the prosthetic valve endocarditis, we are quite concerned about it. So, that

subset of patient, at least in my practice, I tend to use more often.

DR. FERGUSON: Well, I agree with what has been said before. I think the practice is common and certainly probably almost universal in a situation where a valve is being put into a patient that is known to be infected.

DR. CURTIS: I think that sounded to me as I was looking through the information that that might be a particularly high risk group, that it would be interesting to get information about. It is not a common thing. A lot more valves are put into patients who require them because of pathological problems with their valves and don't have endocarditis, but if it were possible to look at repeat infections on patients who were getting a new valve, who had endocarditis, who had one of these valves impregnated with antibiotics, I think there could be -- that might be a group where it might be easy to demonstrate a benefit relatively speaking because they are at such high risk.

Cardiovascular implants, we put -- we are talking about heart valves. I am not sure there is any one kind of valve or position of a valve that there is such a different risk that it matters.

DR. SETHI: In patients who require the bioprosthetic valve, according to the company and the studies done in the past, it has been shown that if you use

antibiotics in those patients, if you soak the valve in antibiotics, you may enhance the degenerative process of the leaflets. So, those valves are not usually being dipped in antibiotics. It is only the mechanical valves.

It would be very interesting to find out if any work had been done in the labs, in the animal lab, whether the sewing rings have been impregnated with antibiotics and then what happens to the leaflet. At least I have no idea whether that work had been done or not.

So, we are talking about two things. We are talking about mechanical valves and bioprosthetic valves, which are handled differently by the surgeons.

DR. CURTIS: Okay. So, there would be much less of a concern with dipping a mechanical valve into a antibiotic solution; whereas, with a bioprosthetic valve, you are concerned about leaflet degeneration. Of course, that would have to be addressed then. I don't know the answer to this either from some of the -- it could be in panel pack, but I don't remember that -- whether or not impregnating a bioprosthetic valve with an antibiotic would enhance or degeneration of the leaflet.

DR. SETHI: It is not in the panel pack. Maybe someone in the audience has done some work on that. I don't know.

DR. CURTIS: Are there any animal studies that

anyone knows of that would suggest that bioprosthetic impregnated, a valve impregnated with antibiotics would degenerate easier?

PARTICIPANT: Would you impregnate the valve leaflets or just the ring?

DR. HOPKINS: I think we are talking theoretically about just the ring or the sewing ring. That is why when we use the antibiotics on the bioprostheses, we just spray it right onto the sewing ring because in the package insert for the biological valves, it is specifically proscribed to dip the valve in the antibiotic.

DR. GILLIAM: It tells you to do it?

DR. CURTIS: Not to do it. Proscribed.

DR. HOPKINS: Proscribed.

DR. SETHI: Whether the leaching of the antibiotics -- you know, I mean, the leaflets have cloned through the sewing ring and if the antibiotic is the culprit to enhance your -- and the antibiotics leaches into the valve leaflet, will that cause problems? I don't know.

DR. CURTIS: That is a good question.

What about aortic versus mitral valves, that sort of thing, is there any difference?

DR. SETHI: I don't think so. At least as far as the technique to implant the valves are concerned, I think they both are equally prone to get infected. At least I do

not know any study where one valve position is known to be worse than other valve positions.

DR. CURTIS: Okay.

DR. GILLIAM: Does it seem like there are possibly three different levels of use of antibiotics? My first view is whether you dip something, whether you actually coat the valve or actually if you make something that -- to me, when you impregnate the valve material, it seems like that all three implies a length of a window, which it might be effective from maybe a few days if you just dip it to maybe a few weeks if you coat it versus maybe even years if you impregnate the valve.

Has there been any experience with anyone ever having an untoward reaction to the antibiotic and the -- have you used some of the antibiotics we don't use all the time.

I know, during pacers, I frequently will flush the pocket with bacitracin, but I don't think I have ever had a person have an allergic response to it, but I am concerned if we have a person, a prosthetic valve or lead or something with, that later the patient turns out to be allergic to. Is there any even anecdotal knowledge of something like that happening?

DR. HOPKINS: I am not aware of any.

DR. SETHI: I think, you know, the experiences are

limited and once we know the patient is allergic to an antibiotic, we will not use that antibiotic anyway. So, actually the question there is you are asking whether we know of any patient, who developed allergic reaction to that. I do not know of any of those patients. But once we know the patient is allergic to a specific antibiotic, we will probably not use antibiotics.

DR. GILLIAM: Well, I guess that is possible. If you are talking about -- even if you are talking about just dipping or coating and you are looking at a matter of days to weeks, I guess the worst cases, you know, you may put someone on steroids even, I guess, for a few days, but if you talk about something that is going to be leaching out in antibiotic for potentially years, I think there maybe has to be a different threshold for looking at that device than something -- you know, if you look at the general practice of just dipping the valve in antibiotics, I feel less uncomfortable with -- you know, everyone seems to do it anyway and it may be what we are seeing, a 1 percent infection rate with, you know -- but I think I would be concerned from a safety issue, you know, what we would need to do to look to see if there are safety issues in something that may dilute a drug for a longer period of time.

DR. CURTIS: Some of the animal studies in here suggested that it was over a period of days to weeks, but

not much beyond that that levels were detectible that you could see any antibiotic.

DR. HOPKINS: As an implant for some devices, certainly not heart valves, I have come to the conclusion that a lot of what we do is sort of black magic and that we do it because we think it will help in terms of antibiotics, in particular. We always treat our pacemaker patients with a couple of -- a day or two or antibiotics. We always flush the pocket out with antimicrobial solution; yet, the data that supports this practice is at best controversial.

My guess is that part of the problem that we are facing is, number one, the likelihood, no matter what is put on the valve, the likelihood is that many surgeons would say -- if it was on a pacing lead, I would say that I want to be extra sure. So, I would probably do exactly what I do now, short of dipping the lead into an antimicrobial solution. But I would probably still give perioperative antibiotics. I would still wash out the wound the same way, so that what we are probably speaking to here is whether this would really change behavior if one of the possible benefits of this is to avoid the use of antibiotics procedurally to decrease the incidence or potential incidence of resistance emergence.

So, one issue is do we ever really ask for scientific evidence to support what has become sort of

discretionary magical response by a lot of physicians in terms of trying to prevent infection, which everybody admits is a terrible problem. It is always a problem in treatment even if it doesn't lead to death.

The other situation, I think, on the exact opposite hand, is that there are no claims made as to resistance or prevention of infection made by the manufacturer. If there is just a comment that these -- that some of these devices will have their sewing rings impregnated with an antibiotic that has been shown in animals, perhaps, to delay infection, is that such an immense problem scientifically for us, that we would require proof of clinical efficacy?

I bring this up in regard to heparin coated stents, for instance, or heparin bonded catheters. If one doesn't specifically make a claim that heparinization does something beneficial, that a non-heparinized device doesn't do, then there seems to be a leeway in allowing for that adjunct to be incorporated into the device without it showing proof of enhanced efficacy would also take thousands of patients to demonstrate.

So, my two concerns here are, number one, how much do we really need to know before we would allow this to occur if no claims are made and, number two, would it really change the practice of the surgeons and the cardiologists

who implant these kinds of devices in terms of their antibiotic use currently?

DR. DOMANSKI: I have a thought about that as a long time proponent of clinical trials and things. I think there are -- you know, not all questions are created equal and I think that the devastation that is wrought by infections in these patients and the relative safety of the use of these antibiotics and the fact that it is rational, coupled with the fact that it would be exquisitely expensive and difficult to study this thing with trials, make this an area where probably controlled trials of this thing are an unreasonable oar to make the folks pull.

So, I think, you know, there is a juxtaposition of three or four things there that I would suggest that we tend to make this hill a bit lower than it is for new devices, some of the other new devices.

The same way with the valves. I mean, clearly, you would stymie new valve development by insisting that the thing be shown to be equivalent because of the very low rate. The valves are very good but if we are ever going to have one better, you need to be a little more flexible than simply insisting that everything needs a controlled trial. And I think we are in a different category than we are with circulatory system devices and things like that.

MS. WHELAN: Could I just maybe ask one of the

representatives how long would these antibiotics be leaching out of the ring? Is that something that is going on for a period of a couple of weeks, like in some of these articles, or is that something that is sort of perpetual?

DR. ANDERSON: That question was addressed a little bit earlier and the idea was that we would have a valve that would release an antibiotic for a year or years. I don't know how we would develop that. I don't think that that is a possibility. I don't think it is possible to develop an antibiotic releasing valve.

Now, you might have a coating but that coating is going to undergo changes in the healing response and that is something that hasn't been addressed and hasn't been considered here, but from my perspective is very important.

So, I would think that if we use the FDA guidelines for devices and implantables, anything greater than 30 days, I think it would certainly fall in that category, but I think based upon the healing response, which we would want -- and let's take a heart valve, for example -- the endothelialization that would occur over the sewing ring there is limited.

I suspect that we possibly could get that in 60 to 90 days and that might be a viable target for developing a system because once you have the endothelial barrier there and you have covered yourself, at least in the annulus, with

antibiotic, then you have to consider that to be fully healed and there would not necessarily be a need. But that is just one design criteria.

I haven't sat down and put all of what I would consider to be biological design criteria into place to put together a hypothetical valve.

MS. WHELAN: That seems to me to be -- something on that time order, it seems to me that it would reduce the risk or the concern about development of antibiotic resistance. Is that a reasonable statement, that if you are dealing with something for several days versus months and months and months on end that the issue is less important?

DR. ANDERSON: We did -- this idea of dipping, I find absolutely ludicrous. I call that feel good therapy. It makes the doctor feel good. This stuff washes out so fast and it is not diffusion. It is not leaching. Those words, don't use them. You are washing -- you put it in a spin dryer and you are spinning that antibiotic right out.

In our -- 20 years ago, we did pharmacokinetics on a device in which the gentamicin was inside the sewing rim in silicone rubber and we put a coating over the surface. We showed that you could get systemic blood levels now on the order of .25 micrograms per milliliter for out to 14 days. Now, that is systemic levels and that is a very, very low measurement for a systemic antibiotic, but we knew that

the tissue levels were much higher.

If you didn't use a coating, a barrier coating on that, we got systemic levels that were below or on the order of 1 microgram per milliliter within two days. So, we even had a barrier there and, yet, it was diffused very, very quickly. So, dipping is -- I don't know how much antibiotic is going to stay there and I don't think it is going to stay there very long and I think it is probably going to be at best hours.

DR. DOMANSKI: Could I just a question about that? I apologize for being ignorant. I am not a wonderful infectious disease person, but, you know, most of the prosthetic valve, the early prosthetic valve endocarditis is felt to be due to contaminate at operation. Would this sort of thing help, dipping help, at least with whatever is causing the very early contamination, the at operation contamination.

DR. ANDERSON: No, I think that we have to consider the process of thrombosis here and what I am talking about is the normal thrombosis that occurs around the sewing rim after it has been inserted because thrombosis and infection really go hand in hand and we have to consider both of them and thrombosis is -- leads to ultimate healing and fibrous capsule formation, if you will, fibrosis, within the sewing ring.

To me, I have to consider that from a pathogenetic point of view.

DR. DOMANSKI: So, if the surgeon is less than sterile when he does it or if the sucker, whatever it is that is producing that early contamination, this wouldn't help with that.

DR. ANDERSON: It might help, but if the patient runs, let's say, a bacteremia within the first 12 to 24 hours, now that is a non-clinical presenting bacteremia, we could seed it in that thrombus and then we would develop -- ultimately develop an infection.

The other point that we have to remember is the healing response that occurs in the sewing ring. This is fibrous tissue and for the most part is avascular. So, we don't have the -- if you will, the inflammatory armamentarium that would normally combat infections in this area. I am not saying that we don't have any vascularity, but I can tell you the vascularity is extremely limited.

So, fibrous capsule formation really is not helpful to us.

DR. GILLIAM: I think, looking at Dr. Tracy's question, though, I mean, even though what I am concerned about, not necessarily since we don't have a product before us to consider, that -- I mean, we are asked to sort of give directions and concerns, not that even though right now

there is no one that has an idea that they can produce something that is going to be an antibiotic diluting device. I don't think we should consider that given the cleverness of the people who are inventing things nowadays, that that may not be a real concern later. I think that we need to focus, though, that there are certain time intervals that changes dramatically how you would consider a device.

I mean, if it is just several days to several weeks, that is one level of concern, but I think once you get beyond that level, there is a concern that I would have that any device that would elute any type of substance. And I think the same concerns that we had early on with the steroid eluting pace release, how long would these leads elute steroids, what would be their systemic effects.

I think maybe that is a model we could somehow incorporate in looking at this lead, you know, elution device.

DR. CURTIS: Well, I am not sure how -- if you had a device that eluted antibiotics for, you know, five years out, why that would be of any benefit anyway if you have something that is totally endothelialized. So, I think what you would be looking at is the initial days to weeks really, early infection.

DR. FERGUSON: Yes, I would think that having an antibiotic impregnated sewing ring would be an improvement

and addition to the things we have already. I don't think it will change current practice in terms of either the surgeons dipping the valve, which I personally think does give some protection from those infections, which might get on the valve, due to breaks in sterile technique.

So, that is one time frame. Then there is the time frame from the time the valve -- from the time the patient is closed, let's say, until the valve is completely endothelialized; that is, the sewing ring. That is six weeks, two months, three months, whatever the time is.

It seems to me that this is the advantage of having impregnated ring for that period of time. So, I think it is a definite addition and I don't think that -- I am not -- my personal bias is that I don't think we need a large clinical trial to permit that to be done.

DR. TRACY: The only concern would be the bioprosthetic valves, whether or not that the antibiotic would somehow get into the leaflet tissue and cause damage there. I don't know if there is somebody here, who is prepared to answer the question what the effects on a bioprosthetic valve would be.

DR. FERGUSON: We have one of the world's leading experts on bioprosthetic valves sitting two places from me.

DR. TRACY: Rosie? No.

DR. HOPKINS: I have a number of thoughts here. I

think the point that has been made about the different time frames is very important. As Dr. Ferguson indicated, the application of topical antibiotics to the sewing ring, I don't think in anybody's mind has any efficacy past a couple of hours. The idea there is just prevent an inoculation of the sewing ring at that point in time.

It also doesn't seem likely that whatever agent is added, whether it is an antibiotic or an antiseptic, would preclude the use of perioperative intravenous antibiotics because that is aimed at a different method of inoculation, which is the septicemia associated or the bacteremias associated with the perioperative experience.

Therefore, I don't think it is going to save money or prevent intravenous antibiotic use. Also, I think the antibiotics versus the antiseptics are very different issues. I think that the antiseptic concept, the silver type of compounds that might produce a very, very prolonged period of anti-bacterial activity at very low levels of local chemical effect is very appealing to affect the long term risk of prosthetic endocarditis and associated with the other things that we do to try to prevent the early spike, seems to me to be very appealing.

The antibiotic incorporation issue is, I think, a much more complicated set of ideas because of the local effects on biological prostheses, because of the difficulty

in really ascertaining what your tissue levels really are, what the rate of degradation of the compounds in the sewing ring are going to be and how it interacts with the allergic response that the patient may have, how it affects the use of intravenous antibiotics in that patient, which ones are compatible, which ones aren't.

Should the surgeon then spray an addition? So, I think there may be slightly different recommendations for these two very different things; an antiseptic application, which may be relatively permanent, versus an antibiotic, which has a short term efficacy.

I also don't think -- and certainly the numbers that were presented to show a response from a prospective randomized trial, I think that if -- it does cause some real difficulty. I think that if the manufacturers can show that there don't seem to be any down side effects to the prosthesis, in other words, there isn't destruction of the valve leaflets in the biological prosthetic, for example, or there is an enhancement of a severe fibrous reaction, where you might get a very thick capsule of fibrous material in response to whatever coating you have there, which might, in fact, cause an increased incidence in prosthetic endocarditis.

I think you could extrapolate from those kinds of laboratory studies a certain amount of safety and proceed

ahead with more of a prospective registry, if you will.

If I recall, and probably the manufacturers know this better than I, but I think we implant about a hundred thousand valves a year. Isn't that about right, in this country.

MR. BENSON: [Nods in the affirmative.]

DR. HOPKINS: So, if, in fact, we followed on a sort of prospective registry fashion just an incident of prosthetic valve endocarditis in those hundred thousand valves for three years, we -- and if every valve was treated with the putative treatment, for example, we would know very, very quickly with the historical relationship to the previous three years whether there was any change in the incidence.

So, a prospective registry type of approach seems more appealing to me as I went through the workbook last week.

DR. CURTIS: Okay. We have been talking about heart valves. I think what we have to think about, too, are things like valves and conduits. What about homografts? What about vascular grafts? Because that is part of what is in this packet, too. We are not just talking about heart valves.

DR. SIMMONS: What about pacemaker leads in patients who have previous infection?

DR. CURTIS: That is a good point, too.

I mean, it seems to me that in all of these cases you are talking about -- except in something like implanting a valve with somebody who already who has had endocarditis, in all of these other cases, you are talking about a situation where the risk of infection should be very low. All of these things you are talking about rates around 1 percent or so. But, yet, when it happens to a patient, it is devastating. It is a terrible problem.

So, you know, there are reasons to want to proceed with some of these approaches. Do any of the other things -- homografts, is there any reason not to? I mean, that is one of the things we usually -- you might consider in somebody who has had previous infection or the valve conduits. Are there any differences there?

DR. HOPKINS: I will address the homograft issue. I think homografts early on had a better reputation than they deserved for the resistance to bacterial endocarditis. Clearly, the resistance to the early phase spike is less in homografts and I think, in general, it is the practice of most surgeons in the country now when possible to use a homograft in the aortic position for aortic prosthetic endocarditis or recurrent endocarditis.

But I don't think that anybody has demonstrated convincingly that there is any late phase advantage to

homografts. Out after a year or so, the incidence per year is approximately the same as the other valve.

DR. CURTIS: Okay. What about vascular grafts? I mean, it seems to me that there would be advantages there, too, to using some sort of an antibiotic impregnation.

DR. TRACY: Unless it has degenerated the tissue.

DR. CURTIS: All right. So, if we had in vitro studies that showed that they held up, then that wouldn't particularly be a problem. So, it doesn't sound like from what we have been talking about -- I mean, it sounds like for any cardiovascular implant, the risk of infection would warrant such an approach and, again, because -- not because the rate of infection is high. The rate of infection is low, but it is a terrible problem for the individual patient if it does occur.

In terms of the potential benefit and the risk of development of antibiotic resistant organisms, I actually really like the approach of using combinations of infrequently used antibiotics in these things because then you -- I don't even remember the names of some of the ones that got put out there, but they are not things we normally use. So, in terms of prophylaxis or prevention of infection, I think that is a really nice approach, as opposed to, you know, impregnating all of this things with, say, vancomycin, if you could or wanted to do something like

that.

I think that that would enhance the development of antibiotic resistant organisms. I think what would be really nice, and I don't see how it could happen -- well, certainly, I think, if these antibiotic impregnated valves and whatever got people away from dipping, I would hope that people would -- surgeons wouldn't consider it necessary to do all of that.

You know, take an antibiotic impregnated valve with two different antibiotics, then dip it in vancomycin and then -- I don't know what -- spray it with something else and put it in the patient. Hopefully, that wouldn't be necessary, although I think that is a less responsible for antibiotic resistance than the systemic antibiotics that are used perioperatively. That, I don't think, would be affected by these antibiotic impregnations of -- because you are -- as you said, it is colonization or introducing it at the operative -- at operation, that is the reason why dipping and that sort of thing is done. But perioperative antibiotics I don't think would go away.

I think it is that sort of thing, the perioperative vancomycin that is more resistant for the development of antibiotic resistance, more responsible for the development of antibiotic resistance than any of these practices in the OR itself.

DR. SETHI: I think, you know, if -- I fully agree with Dr. Hopkins, what he said. It is really nicely summarized. I think he is too optimistic about doctors devoting a day or two for their post-op endocarditis, but that is ideal. In the real world, I doubt that a good registry can be set up where we will -- we or the cardiologists will send the data back to whichever the place is.

If we have got the valve, which is impregnated with antibiotics and we have got -- we feel good about it, I think there will be less usage or maybe there is less usage of vancomycin, less chance of endocarditis. So, we may see that changing.

The second thing is that it is not only -- the endocarditis doesn't happen only because, you know, the surgeon didn't wash his hands, as Mike said here. You have to think about post-op, what happens in post-op. The IV needles that are left in the place, so there is always the danger that -- there is a continuous danger of inoculation of bacteria in the patient when they are in the hospital.

Even when they go home and they come back for their pro-times(?), sometimes I see where the blood is drawn and it really bothers me. So, there are more reasons to develop endocarditis more than just at surgery. There is a high incidence of endocarditis in the first three months.

So, if we can have some kind of antiseptic or antibiotic, which lasts for 90 days or so, I think it will be a good thing to do.

The last thing is to do a prospective study will be extremely difficult, very expensive and probably -- I believe in a study, but I think this is the one place where it probably should not be done.

DR. CURTIS: Okay. Go ahead.

DR. DAROUICHE: May I make some comments, please.

What we learned from our experience with antimicrobial coated central venous catheters that have been proven to be protective in vancomycin prospective clinical trials is that these are what we call as antimicrobial preserved assistants. These are not drug delivery systems. These are antimicrobial preserved assistants that are intended to prevent colonization of the device. And by doing that, very minute fractions of antibiotics or antiseptics are incorporated onto the device.

In fact, the ratio of the total amount of antibiotics or antiseptics on the device compared with a single systemic daily dose of an antibiotic is extremely minute. Now, having said it is important to know that even with an antimicrobial preserved system that provides a rather small total amount of antibiotics or antiseptics, that the concentration of antibiotics or antiseptics on the

surface of the device that is coated with these agents and produces leaching of these agents at a slow, controlled rate is so high that it will prevent colonization not only on the surface of the device but also of the biofilm around the device and, therefore, if you are proposing to have an antimicrobial coated heart valve that is coated with agents, such as alternative antibiotics that will leach off and produce inhibition. In fact, the habit -- the unproven habit of dipping heart valves in antibiotic solution prior to implantation may not be warranted anymore.

However, it would still be warranted if we are dealing with an antimicrobial heart valve that is coated with an agent that does not leach off because if it doesn't leach off, all it does is protects the surface of the device but it does nothing to the biofilm around or the immediate tissue around it.

Now, having said that, I would also like to say that we still have to use systemic perioperative antibiotic prophylaxis because studies actually have shown that the use of these agents, be it for pacemaker insertion or heart valve surgery actually have been treated with lower rates of fluid infection and in the case of pacemaker implantation with lower rates of pocket infection.

So, we still have to use these systemic perioperative antibiotic prophylaxis but if we use an

antimicrobial coated heart valve that slowly has controlled leaching of alternative antibiotics. Most likely, it will allow us to dispense of the unproven habit of dipping in antibiotic and, therefore, allow us to enhance our infection control.

DR. FERGUSON: First, to respond to that, I would think that the matter of dipping is not going to be changed at all in the surgeon's eyes by the fact that he has got the valve, which has an antibiotic in the sewing ring. I think that is a personal issue, but I wouldn't look to that to be a reason that we can save money in the health care system, for instance.

But what I was going to say was that I think we have determined here, it seems to me, that we are not going to have a mechanism in place to prove enhanced efficacy of these new systems. So, what we need to focus on very carefully are the downsides, the dangers of adding these systems to the present devices, which have been approved. We have already mentioned two things, I think, that are important.

One is the relationship in bioprosthesis to the addition of antibiotics to the sewing rings and the adjacent problem that was brought up by Dr. Tracy.

The second one is -- and I think this has perhaps been already proven -- and that is what will the various

substances do in terms of causing the development or overgrowth of pannus around the valve. There are some studies in our packet, for instance, that say there is probably a favorable growth factor, rather than an unfavorable one. That is the pannus is thinner and not as likely to overgrow and cause distortion of the valve function.

I would like to comment, if I may, too, about the use of antibiotics in vascular grafts. It seems to me there we have got a bigger problem than we do -- we have been talking about heart valves all this time. I would feel less comfortable and I need some guidance from the bacteriologists and the commercial people to know whether we are talking about the same kind of problems with a vascular graft.

If you take a 30 millimeter vascular graft and you put a graft in from the asiming(?) aorta all the way down to the iliac arteries, for instance, to take an extreme case, are you exposing the patient to a large dose of antibiotics that would -- I mean, the dose ratio there has to be talked about, it seems to me.

DR. BRINKER: Can I ask a question about infections on vascular grafts? It has been sort of my thought that most of these occur at the suture line as opposed to in the middle. Is that true?

DR. FERGUSON: I think that is true.

DR. BRINKER: And one question -- and, therefore, one could conceivably -- I know you guys cut these things to match, but if one has -- one could conceivably do ends of grafts if they were precut. I know that is a problem.

My other point that I was thinking about -- and I don't know this for a fact -- has anyone thought about leaving the bioprosthesis or the mechanical valve alone, but treating suture material. Is there a predicate for making antimicrobial impregnated suture material?

DR. CALLAHAN: I think what we are going to see is the technology is there to find antimicrobials or antibiotics to most anything. So, that is likely to happen as well. But I don't know that there is any approved for that use yet. But on the concept certainly we are going to quickly go from -- the technology will allow us to do it on any surface. So, sutures would be another one.

DR. BRINKER: In my experience also in the pacemaker project, superficial infections and even delayed ones are almost always associated with sutures. I think that this would be perhaps an easier pill to swallow.

I would like to also just echo that the device isn't made worse structurally by the mode of incorporating antibiotics. For instance, if one develops a polymeric coating of some sort, it is conceivable that degradation of

this polymeric coating that might be used to -- or contain antimicrobial agents would have a detrimental effect either in sizing, spacing or even in structural integrity somehow of the anastomosis.

So, I think that my primary concern is that these devices are no less safe than the unusual device and I would have a much lower need to see a demonstration of efficacy.

DR. SIMMONS: You know, along those same lines, I just wonder, is there any concern about the flow characteristics once you put a coating on some sewing ring or the valve itself? I mean, is there some concern there that flow patterns may not be as good and there may more thrombus or platelet aggregation on these surfaces?

Also, commenting on the registry idea, I guess registries have always kind of left me cold, certainly living through ablation registry era that didn't really lend anything.

Is it as onerous on the companies to do a 5,000 patient postmarket surveillance study as it is to do a premarket 5,000 patient study? I guess I don't know that answer. I mean, could we propose that something on these original valves -- maybe we are going to do not a registry but a required postmarket surveillance that is going to involve 5,000 valves. Is that something that is actually feasible?

MR. JARVIS: I think that is what we are looking for certainly. I don't know how feasible it is. It is certainly doable, but I think --

DR. SIMMONS: Is that onerous on the companies to do something like that?

MR. JARVIS: I am sure they would each have their opinion as to how onerous it is. But the question is -- we have got two levels. Of course, one is if you decide you don't need randomized clinical trials to evaluate the effectiveness, then, of course, what do we need just to allow them to get out there to begin with. And then certainly a registry after the fact in conjunction with that is possible. But I guess we would need to know if you were having that kind of a registry with those kinds of numbers, to want to know why you -- what is driving the numbers. Is it that you really want -- think you need the information and you want it after the fact rather than before the fact or is it --

DR. SIMMONS: I guess, you know, I still have some academic bent in that I guess I can say I am not as -- I guess I am not as concerned about proving that they are efficacious to premarket if I could be assured that it was safe, but at the same time, I would like to know whether this is just a marketing gimmick or whether there is actually some value to this product.

DR. CURTIS: I think that comes up a little bit later about some of the postmarketing studies we could do. You know, we will address that as we go along.

One of the things I wanted to bring up before we get off this first question has to do with questions like, you could conceivably have somebody who has a heart valve in, who has got antibiotics A and B and then gets a Swann-Gantz catheter put in that has got antibiotics C and D in it and then has something else put in that has got other antibiotics in there. You could have multiple devices with antibiotics impregnated into it.

Are there any issues related to that? Does that promote the development of antibiotic-resistant organisms and what issues are there there?

I would like to ask the two infectious disease specialists whether or not they have any concerns about the development of antibiotic resistance with the approaches that have been talked about so far.

DR. DANNER: I am actually not that concerned with these vascular devices in terms of the development of resistance, in terms of adding to the world wide problem that we are all aware of, where our armamentarium of antibiotics are no longer effective against many pathogens and we are not developing antibiotics fast enough to perhaps completely keep up with that problem.

These devices are used in sterile spaces. They are used in situations to prevent infection where inoculum size is very, very low, i.e., in the middle of open heart surgery. Actually encouraging the development of resistant organisms that then get out into the community and cause a public health hazard, I don't think is the main concern.

Those kinds of organisms develop from the use of antibiotics in heavily contaminated, high growth kinds of areas, when you give oral vancomycin for C-difficile colitis and you encourage or cause normal bacterial flora to become, in fact, a super organism that causes -- colonizes hospitals and patients in hospitals and causes problems.

So, I think the resistance issues here are very different. You know what I mean. Again, it is different also than using antibiotics in animal husbandry, where you encourage resistant salmonella in cattle that then breaks out into human populations. This is, in fact, you know, a very, very different resistance issue, I think, than that particular issue.

To me, a bigger concern would be the selection out of resistant organisms that then, in fact, actually infect the device that then makes a very -- creates a very difficult patient to treat because you have now maybe a lower incidence of infection, but the infections that you see may not be responsive to conventional antibiotics and

you have a person who nobody knows how to treat.

Whether that is going to be a real problem with these devices as they are used more frequently is unknown. I think some of that could perhaps be addressed by conducting relevant animal studies that would be analogous to situations where patients might get into that problem. For instance, I think people get secondary infections of intra-vascular devices when they have episodes of bacteremia.

Some of those episodes of bacteremia are polymicrobial and, therefore, would allow the person to select out the organism among that mixture that is the worst one you want to have selected out. There are certainly animal models of polymicrobial bacteremia that you could use to examine what kinds of organisms show up on devices after initiation of bacteremic episode.

So, I am not sure, you know, resistance in the sort of public health hazard kind of thing is really the main issue.

A couple of other quick comments on safety issues. I think the safety issue side of this has been appropriately of major concern that everyone has been raising and I think what we don't know, particularly when a lot of different antimicrobial agents are used on different devices, you know, how will that be regulated without some kind of

efficacy, safety testing for each one? I mean, presumably once the principle is proven and these devices start coming out, there may not be a great ability to control exactly what kind of mixture of things are put on devices.

What we don't know is whether these things would, in fact, create other problems. As we have heard about deterioration of valves, the biological valves, pig valves, are placed for -- in vivo lives of about ten years. Would valves that are impregnated with material last six years or eight years instead of ten? Would there be a small difference in how long they lasted before they became dysfunctional, six months or a year difference, which might be hard to detect unless it was carefully looked for?

Do these coatings, would they delay the endothelialization of a valve so that -- valves are protected from the late endocarditis because they are endothelialized to some degree. So, they become more like normal tissue and have non-adherent surfaces because they have endothelial cells over them.

Does placing this on there -- these materials on there delay endothelialization in any way so that after three months you have perhaps an increased risk of developing a late prosthetic valve endocarditis, even in -- and that risk might be very, very small. It might be hard to, in fact, measure.

In terms of the clinical trial issue, I am not sure a priori that I am willing to just sign off and say that it is prohibitive. You know, we know this works. Why do it? It sounds like dipping is very common. I don't know that impregnating these things through various manufacturing procedures will, in fact, be equivalent to dipping. It may not be as good. It may be that that is exactly what you want. You want very high levels of antibiotics to wash off in the area over a couple of hours and then you did need it anymore, as opposed to having something that lasts a long time.

Some of these antimicrobial agents that are being discussed inhibit protein synthesis. They are selective for bacteria but in high local concentrations, they also have some effects on mammilial(?) cells or might have effects on mammilial cells.

So, though I think it behooves us to maybe make clinical trial criteria somehow easy and less onerous, I am not sure that I am willing to say that we just shouldn't bother at all, probably mainly because of the safety side of it. It would be nice to, even if you don't prove efficacy, it might be nice to see in a thousand patients that you don't, in fact, six months after the device is placed, select out for difficult to treat, unusual flora that you usually don't see on valves or that you don't have, in fact,

in actual vivo situations, where there is a lot of pressure and flow on these devices, that there is not some kind of breakdown or problem, or the issue of allergic reactions if -- you know, my understanding of allergic reactions is that they are not completely dose related and if you put a heart valve into somebody, who then developed a Stevens-Johnson Syndrome and had to take the valve out because they defoliated their skin, that would be a pretty bad event even if it happened in one in a thousand patients.

So, I think, you know, perhaps the bar can be lowered to make a clinical trial possible, but to completely out of hand say they are not needed, I am not really comfortable with that. I am not sure you have to, though, show efficacy at a .05 level.

DR. CURTIS: Thank you.

I think we have covered Question 1 and before we move on to Question 2 --

DR. ANDERSON: Could I make a comment before you leave Question 1?

DR. CURTIS: All right.

DR. ANDERSON: You have talked about vascular grafts, but I would like to make the panel aware of what I think might be an excellent model to study some of these concepts and that is the AV fistulas that are used in hemodialysis patients. In fact, in my retrieval program

from a vascular graft point of view, the great majority of these that are taken on are ineffective.

So, I would also point out that this group of patients has -- I would think, a different risk of benefit ratio or at least that issue would be different with this group of patients. So, when you are considering vascular prostheses, I think we also should consider AV fistulas, too.

DR. CURTIS: Okay.

Dr. Reller, did you want to make any comments?

DR. RELLER: As I listened to the discussion, went over the materials, I am not willing to accept a priori that these devices are either safe or effective. Some of the discussion that has taken place assumes that they are effective and it is better than dipping. To replace an untried, unproven approach to one that -- to replace a senseless one makes no -- doesn't match up with me. I know of no data that dipping anything transiently before putting it in is efficacious.

It doesn't match the sources of infection, the path of physiology as we understand it. For the individual patient, who may develop, now albeit uncommon, endocarditis after a placing of an antimicrobial containing prosthesis, we may have a very difficult problem for treatment of that individual. I agree totally with Dr. Danner that I am less

concerned about the implications for the community.

For the community, I am more concerned about spraying and dipping as a widespread practice. But to gather data after the fact from, you know -- when there is unquestioned but seemingly widespread usage of vancomycin dipping, I think is wishful thinking.

One of the arguments that has been made is the number of patients required because the risk of infection is so low. Well, if the risk of infection is so low and we have an unproved new procedure, isn't the likelihood of benefit also extremely low, the number of patients needed to receive such a device, who would have a better outcome.

So, I am simply unwilling to make assumptions and base recommendations because of the fear of an uncommon outcome that admittedly is very difficult to deal with. There are some things that we do know and that is that antibiotics don't, you know, sterilize these devices. Presumably, they are put in sterilely. Now, the sources of infection are largely owing to things that are done to the patient, as has been pointed out, after the valve is put in and not that one is incorporating the organism at the time of placement of the valve, the things that happen in the perioperative and postoperative and then subsequent period in the early months and then that everyone is at risk for down the line after the initial two months.

DR. DOMANSKI: Maybe I could ask a question about that because my understanding -- and, again, you can take me for what I am worth as an infectious disease person, but my understanding was that the risk of early prosthetic endocarditis is about 1 to 2 percent and it is about the same for late prosthetic valve endocarditis.

I thought that, in fact, it was the perioperative period that was associated with the early endocarditis, which, in fact, is the one with the worst prognosis. And, in fact, if you look at the organisms that are involved, it is more often staphylococcal early and more of it is streptococcal later.

I mean, I am not sure that I -- I am not suggesting that these therapies shouldn't be proven in whatever way you ultimately suggest, but I just -- I guess I don't quite understand. Maybe you can educate me.

DR. RELLER: The early infections are acquired -- I mean, the sources, though, to the best of my understanding -- and this has been recently reviewed with sources of infection in patients with prosthetic valves and it is from the lines and the transient bacteremias, I mean, from other things that are going on with the patients, not that that coagulates negative staphylococcus or less commonly staph aureus, is actually placed right there in the ring at the time that the sutures are placed, that rather we have a

vulnerable device, that then one has the -- the organisms are coming from all the other things that are done, invasive things that are done or the lines that are manipulated, et cetera, the -- on and on and on.

DR. CURTIS: Okay. Why don't we take a break now, 15 minutes.

[Brief recess.]

DR. CURTIS: We are going to move on to Question 2 now. Question 2 reads: If use is justified, it may be impractical to conduct clinical studies with sufficient statistical power, studies too large due to low incidence rates, to support such claims prior to market release. Are there ways to minimize risk without holding up approval of devices, which may offer potential life-saving advantages?

There are two examples here I will just read now. Should use of such products be limited to patients who research at higher risk of infection until further data have been provided? If so, how are these patients identified? And are there creative ways to design clinical trials, which can address patient safety and effectiveness, which would be practical to conduct prior to market release, such as use of historical controls, et cetera? If not, are postmarket studies the only practical alternative?

I would like to start this out by making a couple of comments. What we are looking for with this -- the real

questions are if you use antibiotic impregnated or coatings or whatever on these devices, how do you know it helps? The way you know it helps ultimately is lower infection rates and that is the problem that we have with a low incidence right now, in effect, that we are going to need a long follow-up to find that out.

That is what you are hoping for with these things. The flip side of that, though, and it is very important in terms of allowing these devices to be used is how do you know it doesn't hurt and how could it potentially hurt? I think that is something that we have to get out and think about. I think what I have heard so far are the potential ways it could hurt, are, one, possibility of multiple antibiotic resistance in an individual patient, not a community-wide problem but the concern that even though the infection rate could be lowered overall, that if an infection did occur in an individual patient, the organisms could be worst to treat than usual.

That is a theoretical concern and may turn out to be a practical concern.

The other issue, though, that we have been kind of talking about a little bit is the problem of how would the valve hold up. If we could sure valve function and valve survival were no different with these antibiotics than we have got right now, I don't think there really would be any

concern because the worst case you would have is something that might help and wouldn't hurt.

All right. So, I think the most immediate issue really turns out to be a safety concern is how do you know we are not going to hurt somebody by putting these things in. I think that -- what that starts asking is issues like how well the valve holds up. Are there going to be early problems with sutures coming loose? Or some way that the valve wouldn't function the way you expect it to. Because what you have to think about here is you are talking about a 1.2 percent infection rate. Well, say you lower that by half or so, you would lower it by .5 percent. That means you are going to have one patient out of 200 who doesn't have an infection, who would have otherwise. So, that is who you are helping.

If we even have a minor increase in the rate of valve degeneration, then we could potentially hurt more people than we wind up helping. We certainly don't want to do that. So, I just want to throw that out as something we have got to think about in terms of how we want to talk about doing, you know, premarket versus postmarket studies here.

I will throw that open for discussion. So, we have got Question No. 2 here about ways of minimizing risk without holding up approval of devices and how would we go

ahead and design these clinical trials.

DR. TRACY: Rick, is there an innovative way of looking at these valves and deciding, short of human implants, is there a way of looking at them and telling something about their survival?

DR. HOPKINS: I think if you separate the mechanical and biological, I think, there are certainly biotechnology tests to look at, you know, fabric wear and those kinds of things, just the physical, chemical effect of altering the processing of a dacron skirt. And certainly that would have to be done for approval.

There is also a well-accepted juvenile sheet model for implantation of biological and mechanical valves that could look at -- over the course of the usual 20 week model, that could look at some of these kinds of effects that people are talking about. So that that could be extrapolated to the human situation based upon past experience with that experimental model and looking at things like increased pannus formation and those kinds of sort of mechanical, obvious things that you could grade under the microscope and what have you.

I think that Dr. Curtis has pointed out something and with Dr. Danner's comments that is very, very important now. That is that what if an addition to the scenario is that we reduce the bacterial endocarditis rate by 50

percent, but it is all candida. So, all the patients die. So that if you look at mortality as your outcome, you haven't changed it at all. You may have reduced your incidence of endocarditis, but you have just made it all horrible and they all die.

So, we are going to have to be very thoughtful about the follow-up studies to show that the concept of unintended consequences doesn't play a role here.

But, no, I think there are preclinical studies that could be done -- animal studies that could be done and the usual kinds of physical, chemical studies to look at the alteration and fabric properties certainly could be done.

DR. CURTIS: I am concerned that your first glance you throw a little antibiotic and they are not bad, but if you start changing the structure of the valve ring itself, the more and more you do, the more and more you have to be concerned that you are doing more than just adding a little antibiotic here or antiseptic, as people are saying.

So, we need to start thinking about some of these clinical trial designs. The fact that animal studies or in vitro studies could be done to look at pannus formation, thrombus formation, the way the valve holds up over time, I think those all would be very important to have some assurance that you were not going to create a valve that was not going to wear as well as what we have got right now.

One of the big issues coming up right now is the issue of premarket versus postmarket studies and one of the things about the FDA Modernization Act requires the FDA to consider the least burdensome study design for premarket review. So, if we are going to have premarket studies, it has to be the least burdensome but one that we think is important in terms of safety and effectiveness for a patient.

The postmarket regulations have also been changed and I think we need, you know, maybe a little clarification about what can and can't be done. Certainly postmarket studies are also not supposed to be burdensome, but let's say we just said the animal studies were good, go ahead and start implanting these devices and we will follow the patients up afterwards. We will do postmarket studies to see what the risk of endocarditis is and how patients do.

What happens if companies don't comply? What happens if the data doesn't come in that you were looking for?

DR. CALLAHAN: One thing you have to be clear about is the SMDA and the new FDAMA has not changed the bar really. It is the least burdensome studies to show that the devices are safe and effect. So, it is still the same regulatory process and it is still the same type of decisions we have to make, but what is being asked is that

we sort of look across the type of studies that we would do and require for safety or effectiveness and make sure that we are giving some thought to the least burdensome one. It doesn't say that we should have a lesser standard. We still have to show that the devices are safe and effective.

So, it doesn't really change the way you are looking at things, other than you consider a number of ways and then find out -- you can't, for example, approve a device and then do the study thereafter, let it on the market and then collect the data retrospectively. You still have to address the question, is it safe and effective enough to be there first and then you may still want postmarket surveillance for other reasons. But it didn't really lower the bar at all. It just said that you should look at various ways to address those programs. They still have to be proven safe and effective.

DR. CURTIS: And that still has to be proven before the device can be marketed.

DR. CALLAHAN: Right.

DR. CURTIS: What happens when postmarket studies are agreed upon and the data doesn't come in?

DR. CALLAHAN: Well, there are two different types of studies. If the studies are postmarket -- if it is a conditional approval study, studies are approved on the condition that a specific study is done, then that is

required as a condition of approval. If they don't do it, then you can withdraw approval. The Agency can withdraw approval.

There are other postmarket surveillance studies that can be done in order to find out if there are any differences in the populations or to find out other aspects of the device and then that is a -- I suppose in that case, too, if something happened and we found out that there is some latent effect that we hadn't found, we certainly have the ability to try to take it off the market but the burden of proof would be on us then. But if it is a condition of approval that x study had to be done and they don't do the study, then we can withdraw approval.

DR. CURTIS: I think with this particular set of devices, one of the reasons this was brought before the panel is the fact that proving efficacy beforehand, before market, is going to be extremely difficult if you are talking about thousands of implants and following up a very rare event. I am not sure how we could agree upon a study that would do that prior to market release.

DR. CALLAHAN: I guess there are different levels of proof and that is what we are asking. There is the one sort of gold standard proof that you would randomize control trial and so on. But there are other levels of --

DR. CURTIS: And I guess, you know, we might be

thinking about things like lower rates of colonization and in vitro studies or animal studies that show a beneficial effect. I suppose we could be thinking about that.

DR. CALLAHAN: Or even specific subpopulations that maybe --

DR. CURTIS: Like SVE. Okay.

I think one way we could start looking at this would be to think that perhaps -- since one of the safety concerns is how a valve holds up, there are in vitro studies that could be done. But, perhaps it wouldn't be unreasonable to do a clinical trial of a smaller number of patients like we have had some of the OPC criteria to show that the valve holds up, that you don't have a higher rate of thrombosis, that you don't have a higher -- you know a problem with valve dysfunction. That doesn't require 5,000 patients. It might require three or four hundred patients the way other valves have been looked at.

Maybe that, at least, would allay some of the safety concerns that we have been talking about. Possibly, that sort of a premarket study and maybe one -- you know, the trouble with doing studies in patients with endocarditis is that no one center has got a whole lot of them. You hope you get some, but a study of postop infection rates in patients who are being operated on because of SVE or valve replacements for endocarditis, maybe that is a high risk

population, but one that would have a higher infection -- you know, a theoretical infection rate and that could be studied.

DR. SETHI: It is probably very difficult to do a clinical trial in some set of patient with infective endocarditis. The rate is so low nowadays in our country that it would take a lot of centers to do this study, number one. Number two is that when you offer a patient for randomization, you know, patient, 50 percent of them, they will not sign the consent. So, you are talking about a very prolonged study. So, I am not sure it is doable -- I would think it is doable, but I am not sure it is practical to do it in in a short duration.

As far as the possibility of other complications are concerned, one thing that could be done is to lump all the complications together. That includes thrombosis, thrombo embolism, endocarditis. So, total number of complications may become more and if that group is compared with a another group, then you may need a smaller number of patients, but I am not sure how clean that study is, you know, when you are combining the thrombosis and embolism and infection.

Bleeding should be left separately because bleeding is a complication of usually because of anticoagulation, but the valves complications, which are the

thrombosis, thrombo embolism and valve leak is then put together. Then there is the possibility of at least getting a trend, which are very different in these two valves.

DR. BRINKER: Tom, if a company had an approved valve, which presumably all of these would be modifications of an approved valve and they came to you and said, well, we think we would like to just change the sewing ring a little bit by putting in a different kind of fabric, perhaps, you would consider this on a PMA supplement?

DR. CALLAHAN: Right.

DR. BRINKER: What would be the usual rigor of evidence that you would require for full approval then?

DR. CALLAHAN: You mean, they are putting in another material or they are putting in a --

DR. BRINKER: They are just putting -- let's say a surface material on the sewing ring, they have changed the material to another material that has a history of biocompatibility, it is just a different -- you know, a different selection choice from a menu.

DR. CALLAHAN: Well, we may very well look at just mechanical and animal tests and not do anything further than that.

DR. BRINKER: So, I mean, one thought that -- I think we have to keep in mind, I believe, that all these are going to be modifications to existing valves and that

structurally they are going to be minimal if they are applied just to the sewing ring and I am not sure that what we would require, again, for safety purposes, would be anything more than the kinds of tests that you would use if they were changing that kind of material on the sewing ring.

DR. CALLAHAN: Well, I guess the question is with the antibiotics on there we certainly have had materials -- we have had devices where they have changed surface coatings of materials and have asked rather minimal questions, but in the case of antibiotics, where you actually have the potential for some safety concerns and developing other resistances and developing -- even changing the way people use it or expect to change the way they use practice, that is sort of a different order of magnitude of -- and that is what we hear to ask. Should we be doing something different and on one extreme is saying, well, we really ought to -- unless you can reproduce in animals the same types of microorganisms that you would see in humans, we could do an animal experiment, that you have that extrapolation factor.

You can do the gold standard, which is way off on one end and say, well, because we can't do that, we want to do randomized controlled clinical trials, but if that seems too much, isn't there something in between OPCs? What I hear you are stating is that it could be done just with the way we do it in a PMA supplements, but that is the kind of

guidance we are asking.

If we do it that way, do we need some clinical data if we do what and what are the areas of concern. How we handle it, whether it be a supplement or a whole new PMA, I think -- there may be devices that come in with -- that we have never seen before and for the first time and they will get the standard clinical trial for a heart valve.

DR. BRINKER: Which is appropriate because you are looking at greater structural and functional characteristics, but conceivably from what I am hearing, most of what is changing is going to be --

DR. CALLAHAN: I think that the deeper question is if someone came in right now with a new valve and they had no antibiotic coatings on the outside, then we would use the FDA guidance to go through and we would look at various things. We would look at infection rate and we would see, well, as long as it is not more than that and the question of 1.2 percent endocarditis and fell within that guide, we would say fine.

The question is if you then came in the first time with a new valve and had an antibiotic on it, should we be doing more than that or should we just be doing the same sort of things and saying, well, it is no different then. That is, I think, the --

DR. BRINKER: Well, actually, that is a nice

model. If a person came in with a new valve that had an antibiotic on it -- well, that did have an antibiotic on it, what is the size of the clinical trial to meet the OPCs that you would -- that you standardly ask for?

DR. CALLAHAN: I could use 350. We just did that.

PARTICIPANT: It is 800 valve years.

DR. BRINKER: It is 800 valve years is what it -- I mean, that would be the simplest of all issues, it seems to me, because that kind of follow-up would -- if a company came in with a new heart valve that just happened to have an antibiotic on it, I think that the same kind of questions for initial safety could be answered with 800 valve years certainly.

The more difficult question is is a company that says I have had this valve. It is a great valve. It is state of the art. You know, 90 percent of the aortic valves happen to be this valve in this country now in the mechanical valves at least and we want to change the sewing ring so that it incorporates a little bit of this in it.

Then what is the requirement? And is that a PMA supplement that would be covering or --

DR. CALLAHAN: How we handle it is sort of a -- it probably would be a PMA supplement, but that is really not the panel's concern. The question is should we be doing anything different with that kind of a scenario that is

brought before the Agency. That is why we are here, isn't it? Those situations are coming up.

DR. CURTIS: Are we still using the old PC criteria for the heart valves because there was a discussion about that last fall and a lot of the data was kind of old.

DR. CALLAHAN: Right. We have talked about -- we are in the process of amending that and we have been working in house, as well as with HIMA on the outside to update that, but as we speak we are still using it. But we are in the process of changing.

DR. GILLIAM: It is kind of hard to imagine that a person can talk about a valve that has got a proven track record and if they wanted to add an eluting agent of some sort to the valve. The would actually have to go through more testing and procedures than they would if they were starting a totally new valve. You know, I think if we are going to really look at what is going to be reasonable to ask companies to go through to prove safety of an antibiotic impregnated valve, then the way we have always done things, you would think that it would be less onerous than it would be to present a new valve to the Agency.

So, I am not sure whether that is right, wrong or indifferent but somehow it seems in keeping that it should be easier to take a valve that you have a good track record on and do this and perhaps look at it postmarket.

Postmarket, however, I think that obtaining the data is the key to it all. I mean, if we are going -- if we wish to do a postmarket follow-up to make sure the valve is still safe and that is our only concern, then it may very well be that on a lot of the valve, prosthetic valves, it may take six or eight years before we find out whether their leaflets faster than the ones, which are not.

So, I mean, it would -- I think what we are really talking about is are we willing to make the whole thing from postmarket and we are going to follow everyone of these valves or a significant portion for the life of the valve until we can get this information or not. Or are we willing to just find out whether it is safe. I think if we are following for long term, we will find out within six months afterwards whether the thing causes more or less infection.

If you follow a hundred thousand valves for six months, then you would have the answer right there whether it was -- the incidence of infection was any less than the ones at least in the first, you know, implant period. But I think that doesn't answer the safety question. You would have to follow them a lot longer.

DR. BRINKER: Well, first of all, we are not going to get a hundred thousand valves because only one company presumably will vanguard this and they are not going to have a hundred thousand valves, but I think that some of the

other issues are clear. I think that the tissue valves should probably be considered separately than the mechanical valves for this particular question.

I think we would need some input from the company whether it is -- from the companies that want to do this, whether they would think that the equivalence of a OPC kind of study, 350 patients for two plus years, is an onerous responsibility to fulfill because I think that certainly that is much less than the 10,000 patients and the 1,000 patients and 5,000 patients that were suggested might be necessary for a randomized trial and it would seem to satisfy -- if it satisfies a new valve, it would certainly satisfy in my mind this problem.

DR. GILLIAM: I think that is wrong, though. I think -- I may not have been very clear. I think the reason that I am concerned about using the previous OPC for this is that we are talking about something we have no clue as to other -- I mean, we sort of took the old valves and we had certain things we watched for and when someone presented a new valve, we knew the rules. So, we watched for the valve to fail.

Now, we potentially may have other problems with putting this drug elution system, if you will, within the valve that may cause product -- things with the product that we have never tested for. I am not saying it was right or

wrong. I think that it may very well be that 350 valves may not be required at all. Maybe it doesn't require that many to find out whether it is safe, but then we may have to do something postmarket for a lot longer period of time than we have now.

DR. BRINKER: I agree with that. I am just saying that for the buy-in we need a reasonable confidence, clinical confidence, that the device is safe and effective.

DR. CALLAHAN: It is the last part, too, which is heavily dependent on what claims the manufacturer wants to make.

DR. BRINKER: The best scenario would be if they made no claims as to efficacy. And that is not -- I mean, we have gone through this before with other kinds of adjuncts that there is no specific claims to efficacy, but there is some description in the labeling that in certain scenarios in animal studies or what have you there might be some benefit.

DR. TRACY: But there are two aspects to the safety and efficacy of what we are talking about. One is the mechanics of the valve, the function, duration of its longevity and so on and so forth. And the second is the affects of the antibiotic in the system to the person, to the infection.

If I heard what Rick said right, you probably

could test the mechanical aspects of the valve, pannus formation and so on, in an animal study or a bench study. Personally, I would think that that would be satisfactory, especially if you are dealing with a valve that has already been manufactured and proven to be a quality product.

The second issue is the issue of what does the antibiotic do and the question, I guess, is does anybody feel that it is worse than sticking it in an antibiotic solution, which is for better or worse the predominant practice in this country?

What would be a reasonable expectation to prove that it is not worth then what we do with currently available valves, sticking them or spraying them or whatever and how long do you need to -- if you have got a low rate of infection as it stands, how long are you going to need to follow a product to determine whether you have reduced it by x percent. Is that reasonable or is that something that is better done by postmarket surveillance?

DR. CURTIS: Well, I don't think there is any way that there is going to be a clinical study done to show a change in infection rates prior to market. It is just -- it is too huge. You have got a 1 percent rate you are trying to reduce. You will never be able to do that. So, that is just not practical.

In terms of trying to get back to the questions

here, I think there is a consensus that in vitro and animal studies to show several things. One is the valve that seems to work the way other valves have in the past and their rates of colonization are lower would be good things to have ahead of time.

In terms of whether or not patient studies would need to be done, I am not sure that I think that just because there is an antibiotic in there makes the valve so different that that in and of itself requires 400 patients or 300 patients to be studied for x number of months the way we normally do that.

I think that is kind of a judgment. To me it is a little bit like, you know, changing the material on the sewing ring. How different is it from the currently existing valve? If that is all there is a little antibiotic, I am not sure it requires that, but I mean that is kind of a judgment call there.

DR. SIMMONS: If I could just put my two cents in --

DR. CURTIS: Go ahead.

DR. SIMMONS: -- is that I would say that you don't know. You just don't know. This is the first time this material has been introduced in a permanent setting and you don't know what is going to happen. So to say that you are willing to accept less than what a regular new implanted

valve that comes off the shelf is going to take just doesn't quite make sense to me.

It may be, you know, not fair but the very first company that brings this thing to market is going to have to bear the burden that this is brand new. And at the very least you have got to do the 800 patient years, I would say.

DR. CURTIS: All right. Well, let's say that we are done and it showed that there weren't more problems with thrombosis and, you know, the usual things, the OPC type of criteria that we have used and realizing that it is underpowered to see a difference in infection, that would seem to me to be probably acceptable to a majority of the --

[Multiple discussions.]

DR. SIMMONS: -- the next antibiotic, do it all over for them?

PARTICIPANT: The next antibiotic is a different situation.

DR. BRINKER: No, it is not a different situation because it is likely that each of these companies are going to use a proprietary method of putting the antibiotic onto the device. Using your thinking, then every proprietary mechanism for putting the antibiotic on has to be retested.

DR. SIMMONS: I will grant that. I agree with you.

DR. GILLIAM: And potentially every antibiotic

will need to be tested under this level and --

DR. CURTIS: Dr. Reller, did you want to make a comment?

DR. RELLER: I would like to comment specifically on the questions at hand. The first, on 2(a), I don't think it is practical to identify patients at higher risk to settle issues of efficacy of the valve. This assumes that we already have proved efficacy and by selecting patients, one could demonstrate it unequivocally because of higher infection rates, but those patients, one could consider those who are having a valve replaced because of current endocarditis with appropriate debridement, the infection rates actually with great surgery and intensive antimicrobial therapy that is bacteriocidal or fungicidal for the specific organism, the infection rates are not that much higher, if at all, in some series than placing a valve without infection present.

So, I don't think that is the way to go and it assumes that you have already demonstrated efficacy, which I don't -- which we haven't.

DR. CURTIS: Well, see, I don't agree with that because, I mean, the only point in picking out a population like that is that you would like to think that, you know, since the hypothesis is that it helps, you are trying to select a patient group that would have a higher rate;

therefore, you really need a lower n.

So, I don't think it has to assume efficacy ahead of time, but I understand what you are saying. And I agree, I don't think we can find a population like that.

DR. RELLER: And to tease out the component of the antimicrobials in the valve ring versus the kind of intensive systemic therapy these patients are getting, I don't think the answer is going to come from such a group of patients.

2(b), to me, the minimum standard that these valves should meet with antibiotic in them is the performance criteria for a new valve, minimum. And that precludes just depending on postmarketing studies. I think that is wishful thinking. We are not going to get the information. There have been legitimate concerns of safety raised and that a valve that has antibiotics incorporated somehow, some antimicrobial, does as well as a currently marketed valve is expected to perform, I think, is minimum.

If one wanted, in addition, that is, a firm wanted in addition to claim that infection rates or any other component of this new valve or new formulation of a valve did something that its predecessor without the antibiotic did not do, I don't see any way of being able to claim that without doing a study that shows it.

Now, whether these things should be kept off the

market is another issue but if they are put on the market, then at least they should be functionally as good as and as safe as with no more infections than what is sold currently.

DR. CURTIS: I don't think the historical control issue helps here, except in the terms of the OPC, the objective performance criteria or whatever modification is going to be used and comparing how the valves hold up now.

So, really I agree in terms of (a). I don't think you can select a population that is going to have a higher infection rate and design a trial and have that work out. But it sounds like there is a consensus that doing only postmarket studies would be inadvisable.

DR. TRACY: Anne, are we saying or are you saying then that you expect within time period of assessment for these valves as though they were new products, that you would find -- you would get the answer to your original concern that you have that somehow these were going to make -- both of you raised this concern that there would be a worse potential component, an individual patient -- are you going to satisfy that within that time period of evaluation, the 800 patients?

If not, then what is the point of it at all if the company is willing to -- is not marketing this as something that reduces infection?

DR. DOMANSKI: You know, it makes me a little

nervous to -- you know, I understand the sort of slight of hand of talking about not making any specific claim, but I guess I worry a little bit about, you know, that begging the issue. That is, I think one has to say it is rational -- you know, if you are going to do just postmarketing stuff, it seems to me you have to end up just saying that it is rational to suppose, you know, given the historical data that this may, in fact, reduce infections and we are going to follow this in postmarketing with some kind of clever thing, but I think there are just --

DR. CURTIS: That is not what I am saying. I am just questioning whether or not within the typical analysis that would be done for a new valve, you would answer the question. I think you would not. So, I think that regardless you are mandated to have an excellent postmarket surveillance. So, the question becomes what level of proof is necessary before marketing.

DR. DOMANSKI: Yes, and it may be that a rational -- you know, a rational understanding of, you know, what has gone on historically with these catheters is enough, that this may not be a massive change in the catheter that requires a massive study prior to letting it go out on the market.

DR. FERGUSON: I would also add, I think if we determine that this is a brand new valve and has to be

treated as such, the data that we collect for those is going to not be the data we are looking for, which is sort of what you are saying, Cynthia, I think, in terms of the addition of the antibiotic.

I mean, we are going to be gathering a lot of data, which would be nice to have, I guess, to prove that the deterioration rates are the same and so on, in the case of bioprosthesis and mechanical valves, the incidence of fracture or whatever else you want to do that we go through for those valves. But those are all things out here that are different from what we are talking about.

DR. CALLAHAN: There is also an underlying question that Mike, I think, was alluding to a minute ago and that is, you know, you can sort of dance around the issue and say we won't make any claims, but the question, I think, before us as well is why expose patients to any risk if you can't show a benefit.

DR. CURTIS: That is what I was just thinking, too. I mean, you probably could show a reduction in colonization of valves with bacteria in animal studies. I mean, this sort of thing has been done in the grafts. That would be -- without a very large study, that would be the only thing you would be able to say before market release, assuming you did the trial to say the valves hold up just as well. So, you say, you know, the valve holds up just as

well. It reduces colonization.

You hope it is going to reduce infection but you don't know. So, you do, you know, follow the patients up -- you follow up five, ten thousand patients postmarket and the infection rate is 1.2 percent, exactly the same as not having the antibiotic in the valve. Then what? I mean, then you have something that is not effective.

I don't know where that leads us but I mean --

DR. GILLIAM: But if it were not effective and they did not make the claim that the --

DR. CURTIS: Why are we doing it?

DR. GILLIAM: Well, I mean, it is not we. It is the industry --

DR. CURTIS: Why is it being done?

DR. GILLIAM: The industry was being questioned because, obviously, it would cost them money to do it and I would imagine if they found it was ineffective and they couldn't get a marketing claim, I think we will let the market take care of it and they probably will stop doing it.

I am more concerned that if we look at, I guess, what I sort of feel we are here for is to try to give them guidance on how to set up this technology in such a manner that companies can incorporate it and if it happens to be a good thing for patients, how can we more quickly incorporate it in our present devices; at the same time, not sacrifice,

you know, at all any safety issues.

Assuming that it is not going to be worse than we have, what is the quickest way we can get it and if there is any good, to show it. So, I think I am more inclined to think that the initial safety studies in animals are going to be helpful, but I am still concerned because if I were a company then looking, I would say, well, I will take my mechanical valves right now and no one seems to be talking about that there is potential safety concerns for the mechanical valves, but I think there are concerns for them. I mean, we don't know the local reactions and how it will affect the implanted patient. I think those data may not be so easily obtained.

DR. CURTIS: The one problem, though, with, you know, just looking at infection rates postmarket is if there is a valve out, it has got an antibiotic in it. It reduces colonization. That is all it says. Nobody is going to want to do studies showing that it lowers infection rates because you have already got -- I mean, everybody is kind of going to be the mindset that -- you know, it is like flushing bacitracin in a pacemaker pocket. It might help.

DR. GILLIAM: But I think that is why, you know, I think what Tom put out -- I think this is one of those situations where as the Agency, we would have to say this product must have a study, which must collect the data

postmarket and then that data has to be -- you know, that may be where you do your trial, where you do, you know, give conditional approval to demonstrate that there is, in fact, not something that is dangerous.

DR. HOPKINS: Tom, can I ask you a question? The St. Jude valve is now becoming available with a silver impregnated sewing ring.

DR. CALLAHAN: Right.

DR. HOPKINS: How did that -- where did the approval from the FDA come for that and in what mechanism and how does that impact what we are discussing today?

DR. CALLAHAN: Dr. Brinker passed out something earlier. There are other products, including the St. Jude that you mentioned, that have had not antimicrobials, but antibacterial, those kind of things and we have had a lesser standard for them.

So, the question here is really directed toward antimicrobial. Is there more risk to exposing a patient population to antimicrobials, you know, the coating, than an antibacterial, like a silver --

DR. HOPKINS: Tom, could we ask why that decision was made that way, to say that the silver impregnation was okay and antibiotics wouldn't be okay? I mean, aren't they in sort of the same category?

DR. CALLAHAN: Well, we had internal talks about,

you know, whether that is enough, but something that can really affect a whole population of bacteria and help colonize -- allow colonization of a new type of bacteria is felt to be in a different kettle of fish than silver diazine or something like that. And it is probably not unlike the very, very low levels that we have had other coatings that even don't -- are not antimicrobial. They are just surface property coatings. But that is the point at which we are getting uneasy and we think we to ask, you know, the clinical community are we stepping beyond. Maybe it is a continuum. Maybe then we don't need to worry anymore, but are we stepping beyond when we go to an antimicrobial and are we exposing patients to a lot of risk that we weren't otherwise doing.

DR. BRINKER: One thing for me, having just been aware of this issue, changes a bit some of the thinking in terms of what we are trying to see with even an OPC trial. I know one of our concerns were that this coating or change would affect the way the valve functions. Now, that doesn't depend on whether it is an antiseptic or an antibiotic. If it is a coating, presumably it is a coating.

Now, albeit, there may be some polymers or something else that are incorporated that very well may change it. The fact of the matter is that the Agency in my mind, by allowing a change in coating, even if it is an

antiseptic, without the concern that this may somehow change the rate of endothelialization or any of these other things clinically makes me less concerned about the characteristics of a mechanical valve and focuses attention on what special aspects the incorporation of an antibiotic has over the antiseptic.

That really focuses the discussion separately because you have already -- in my mind, you have set a standard in a way.

DR. HOPKINS: Yes. I would like to go back to something I said earlier and I think this exactly does focus. I think the issue of an antiseptic modification of an already effective sewing ring in a mechanical valve is a very different issue than a prolonged antibiotic elution mechanism in a biological valve. There is a clear difference in the kinds of things that might be happening.

So, I think it is important that we as a panel perhaps agreed to separate these to a certain extent and begin to hone in on what we would expect should be required from the more concerning components.

There is some evidence, for example, that silver impregnation at the right dose has a beneficial effect on pannus formation. So, in that particular example, there are some pretty good animal studies to support that the material properties are not altered and, if anything, improved. And

the consequences to a mechanical valve, a negative down side, are pretty -- from an armchair standpoint, pretty minor.

So, it may be that we as a panel are going to have to recommend slightly different approaches for mechanical valves versus the biological valves and slightly different approaches for disinfectants versus true antibiotics. And that there would be a spectrum of premarket requirements versus postmarket surveillance type studies for sort of the four paradigms.

The other problem is we are also looking at early phase and late phase events. We are looking at early phase infection and early phase failure and we are looking at late phase infections and late phase failures. And as Dr. Curtis pointed out, the late phase stuff, if you look at the knee on the curves for biological valves, they sort of vary, from about seven years out after implementation, they start to deteriorate at somewhere around 12 to 15 years, depending on which valve you are talking about.

We are never going to get that data in time to be of benefit to the industry. That is going to have to be a postmarket type of a study, to look at the durability issues of the valves when you get out that far. What we are trying to head off is some unintended disaster that would cause a 5 or 7 or 8 percent increase in valve failure rates in the

first couple of years.

That may be discernible from a relatively small study, a pilot study of 100 or 200 patients who are followed for one to two years and that we could say with some assurance some totally unexpected, unintended problem has not occurred in the first year or two. So, the power of that would be, perhaps, one-fourth or one-sixteenth of the OPC, but at least we have proven that some horrible disaster hasn't occurred.

So that in my thinking, the mechanical valves with disinfectants probably can be done with the animal studies and the data to date and can go forward as you have already done in at least one example. If you are talking about putting an antibiotic in a biological valve, at the minimum, I would want a patient study of a couple of hundred patients, who are followed for a couple of years to make sure that some really horrible early phase event is not occurring. And that would provide protection to our population that we are expected to provide.

Then mandating, I think, in all cases some form of postmarket study follow-up, which we can -- there are further questions down the road, I think, that address that.

DR. GILLIAM: Anne, if I could just -- referring back to the material that we were given, specifically relating to the St. Jude silver impregnation, I mean, the

work that they did according to the paper was that they have shown that the coating is tightly adherent to the cloth. It is low leaching and it is effective in inhibiting colonization on the cloth by microorganisms, which were introduced purposely, experimentally, to mimic infections in the human.

It doesn't take a quantum leap for me to use the same type of experimental studies where an antibiotic is added if the assurance of our colleagues from infectious disease will tell us that we don't have to worry about Stevens-Johnson Syndrome or we don't have to worry about patients becoming sensitive.

From what I have heard so far and what I have read so far, I think those concerns are very low. So, I don't have much difficulty in saying for at least for this particular situation -- I agree with Rick about the bioprosthesis a lot and I am a little concerned about this, transposing this kind of experimental data to any other situation, other than heart valve rings, tissue, the cloth ring. By that I mean I would -- it makes me a little bit more nervous to talk about using this experimental type model for cloth grafts that are going to be put in. I think that is another situation.

DR. CURTIS: Okay. I think we have kind of beaten this one into the ground. Just in summarizing I would say

that, no, we don't think that postmarket studies are the only way to go here, that in order to address patient safety issues, premarket studies would need to be done, but a small study on the order of whatever it turns out to be, two or three hundred patients, that sort of thing, to demonstrate that there aren't the potential disasters, as you mentioned, and that patients would have to be followed up.

I think that leads directly into Question 3. So, if we can switch to that now -- if postmarket studies are the only practical alternative, which I think we have -- if I can speak for everybody -- agreed on, that probably is true in terms of proving -- ultimately proving lower infection rates for endocarditis certainly, what premarket studies should be considered in determining if the product offers the potential for reducing infection and does not pose undue risk to the patient?

I think we have more or less answered this for the heart valves.

DR. ALPERT: If I may?

DR. CURTIS: Yes.

DR. ALPERT: I think one of the particular issues here is both Dr. Danner and Dr. Reller commented on the risk to an individual patient in selecting resistant organisms when a patient gets infected. The question that I would ask them is do they have some thoughts on the kinds of

evaluation -- the general evaluation for the incidence of infection isn't going to answer the question as to whether there is a risk posed to individual patients, who develop endocarditis.

So, one of the questions is are there studies -- is there a study model or are there studies that should or could be done to address that aspect of risk to the individual who gets infected because that is one of the issues, as well as the concern about the kinds of drugs that ought to be or ought not to be evaluated in this setting.

We have raised the concerns about from the valve aspect worrying about the impact on the bioprosthesis. We have talked about the issue of worrying about whether the ring is going to hold up and whether there is any degradation that takes place. But I think we also have to look at the choices of drugs and their impact on the individual patient, who does get infected because that is really where -- as was discussed by the infectious disease folks -- the real risk that these anti-infectives may have.

Silver doesn't pose that risk. So, the question is now going into an antibiotic, into a very different model, that risk is real.

DR. RELLER: For the individual patient, I am not at all convinced that incorporating the antibiotics that have been offered in these valves are wise in the first

place. I think that we sort of move into the critical issues that have been pointed out. If there is no reason to use these, other than reducing infection, then, you know, we ought to show that it does that.

For the individual patient, regardless of what is decided, I think that it would be very important that every patient who develops infection after placement of such a valve, if approved or allowed to be studied, that there would be need to be surveillance of all episodes of endocarditis after these valves.

What one would look for would depend on what antibiotic was incorporated in the first place. Obviously, what one would be most interested in is does the patient have an untreatable infection, either a fungus or a multi-drug resistant organism because of the specific antibiotic that was incorporated into the valve.

Antibiotics that I would be -- think it would be ill-advised to put in the valve, two come to mind straight off. One is vancomycin. Currently and in the foreseeable future it is -- for the most common organisms, it is the only thing that we have that works. It is a great anti-staphylococcal drug, but if the staphylococci are resistant to other things, it is currently the only thing that we have of demonstrated value.

Secondly, sometimes things happen that one doesn't

expect. I wouldn't want to see gentamicin in these valves. It is pretty clear that the high level resistance to aminoglycocides in enterococci that render some strains of enterococci that cause endocarditis very difficult to treat because of high level aminoglycoside resistance and, therefore, not being able to achieve synergy with penicillin, quite apart from the vancomycin-resistant enterococci that are almost impossible to treat with serious infections like endocarditis.

It is likely -- and some people believe that these organisms were fostered by the use of topical gentamicin therapy for burns and oral gentamicin for prophylaxis in surgery, that had a brief period of use and then was abandoned. I mean, the plasmids that carried these inactivated enzymes in enterococcus came from the staphylococci and they were selected with topical use.

So, I don't like the idea of putting gentamicin because we need the aminoglycosides for some other infections. And many staphylococci are already resistant and they are only adjunctive therapy anyway, not, of course, primary therapy.

Then one gets into rifampin. One of the cardinal principles of therapy and prevention is the presence of bacteriocidal therapy at the time the procedure is done. I mean, this is a proven surgical prophylactic principle. And

for therapy of endocarditis, in addition to the debridement and all of the other things that are so crucial -- I mean, what has enabled these phenomenal strides in treating the infective endocarditis is great surgery and bacteriocidal antibiotics.

There is no staphylococcus that has ever, ever been killed by rifampin. Putting rifampin in these valves makes no sense to me whatsoever for the kinds of organisms that cause infective endocarditis in prosthetic valves. Combining rifampin with tetracycline, well, tetracyclines don't kill staphylococci either and I know of no data that there is any synergy between rifampin and tetracycline.

So, it is putting a betalactan(?), will they hold up, and then one has the sensitivity issue. So, it is actually quite difficult in my mind to come up with a plausible antibiotic that I would want put into these things in the first place even if they did work, which I am deeply skeptical about.

So, I think there are lots of pitfalls and the things that would theoretically, if efficacy was shown, be best are the very things that we now have only to depend on, along with good surgical technique in the therapy of prosthetic valve endocarditis.

DR. DANNER: Actually, I would like to ask a question before I answer your question.

The industry had said that doing an appropriate clinical trial would be overly burdensome for them and the implication is is that a potentially useful new or altered device will then not be available to the American people because -- if that is required, because this is just too burdensome and they can't do it. The FDA, at least from comments being made, have bought into that, it seems to me.

What is the criteria for that? In other words, what determines when a trial is overly burdensome? What is the industry criteria for making that financial decision and what is the FDA's criteria for making that regulatory decision?

DR. DOMANSKI: You know, one thing in listening to this discussion is this is a little bit different than what we are used to hearing about. I mean, we are usually -- we listened yesterday to a discussion and tried to decide whether some device was effective or something was reasonable evidence and then we tried to decide whether it is safe enough and so forth.

You know, clinical trials aren't going to pick up some of the things that Dr. Reller is talking about. I mean, if he is worried -- he is reasoning from first principles that this isn't a good idea as we were reasoning from first principles that it is probably not all that unsafe to do it. I mean, what he is saying, I think, in

effect, is that one of the problems that you won't pick up with a clinical trial or premarket surveillance or postmarket surveillance is the development of resistance because of the widespread use of these things.

I mean, I am concerned that maybe it is not just a methodologic question, that it is just plain -- I am beginning to wonder whether it is a bad idea from first principles to do it at all. And I wonder what the thoughts are about that.

DR. CURTIS: Well, let's get back to what Dr. Danner mentioned. Maybe you could take a stab at that, Tom.

DR. CALLAHAN: We are dealing with a new law that just was promulgated and we just got it in February and we don't, any of us, have any operable definitions for what is least burdensome. So, we are trying to do this on a day-by-day basis since we were given the charge to make it least burdensome.

What we are trying to do is look at the whole field of things that we could do. I don't think we have changed our mark, either higher or lower yet. We are just trying to look at all the possible things that could be done and make sure we have exhaustively looked at the types of trials and then make some judgment based on that.

DR. DANNER: Maybe I can ask the industry this. I mean, am I making the right assumption that when you make

that kind of decision that you are basing it on how large the market is, i.e., how much money you can make by putting something out in that market versus how much it costs you to do the trial? Is that correct?

PARTICIPANT: Yes, that is reasonable. And one thing that we came here and said is that the sort of four and five thousand patient years that Dr. Naftal had presented to prove efficacy truly would be burdensome. We simply could not afford to fund that sort of a clinical trial. We certainly couldn't recuperate our expenses from that.

We are here also to talk about what could be a reasonable --

DR. DANNER: Well, I have no idea what your estimates are on the size of this market, but if you did a trial with, let's say, 2,000 patients, a randomized trial and you did that trial for one year to look at some of these allergy issues, resistant organisms and if there is, in fact, a shift in the pattern of the disease you see with the alteration in the valve, if you did that kind of study, how much would that cost and would that be burdensome to do?

In other words, you know, if you look at some of the dipping data, which I agree with Dr. Reller is very -- not very convincing or good data, but if you look at that data, it suggests that perhaps the efficacy of this might be

better than 50 percent, at least in terms of early endocarditis, which you have a risk for or a high risk for two or three months.

Your estimate was 50 percent but some of that data looks like the efficacy might be more like 80 percent or 90 percent, which, of course, reduces the numbers that you need in order to show efficacy. Also, if you change the level of burden, i.e., if we only wanted to be 80 percent confident that there was efficacy, as opposed to 90 percent confident, that would also reduce your numbers.

By playing with those kinds of things, can we, in fact, get to something you can afford?

PARTICIPANT: I think we are headed in the right direction.

David, do you have any thoughts on this?

DR. NAFTAL: No. I am just sitting here enjoying the discussion and I agree with you totally. If you backed off from the power a little bit, you know, you can make adjustments and make it less just overwhelming. Of course, there is less chance that you will find something significant. So, you may have to back off the .05 level, go to .1 or something.

But, yes, any changes like that make dramatic differences in these numbers that are required.

DR. DANNER: Then that gets to the question that

was asked, which, you know, we have already talked about that one of the issues is durability and the difficulty in answering that, at least long term, the antibiotic specific issues tend to center, I think, around the possibility for local or systemic allergic reactions, certainly any kind of reaction that required you to have -- be re-operated on within a couple of weeks would be a disaster. Even if the incidence of that was one in a thousand or one in two thousand, you wouldn't want to see that.

There is the issue of selecting for resistant organisms and I think that is a real one, particularly once you get to the point where valves are being infected by bacteremic events in people, as opposed to contamination at the time of surgery, because those bacteremic events are probably polymicrobial and you might be selecting out for the worst of your choices in that kind of setting.

The other would be whether there is an effect on endothelialization so that the valve -- I mean, my understanding of endothelialization is that for late endocarditis anyway that endothelialization of valve protects you somewhat and probably is part of the factor that is shifting the flora that is attaching to the valve.

I guess those last two issues raise the question: Will putting in this kind of valve change the disease? Will you have a different flora? Will it occur at a different

time and will you go from not having it early, but getting more late or something like that?

The allergy issues, I think, are difficult to answer, you know, and that probably will depend on the antibiotic you choose and the specific -- how it is put on the device, how much actually leaches out from the area. So, I think, you know, that is certainly unclear.

In terms of deciding which antibiotics you choose for this and which are the safest combinations or the best combinations, I am sort of left in the same problem that Dr. Reller is in that I really have no data or experience to base those decisions on in a particularly rational way. I mean, resistance is passed by plasmids often and plasmids contain -- can contain multiple antibiotic resistance genes. So, if you put even a -- if you put one antibiotic on, you could actually select for resistance to multiple antibiotics or even unrelated potentially.

So, I think that is a complex issue and the way -- the only way for me that I can get past all of these safety issues and maybe also get some information on efficacy is with a clinical trial. The clinical trial maybe doesn't have to show efficacy at a .05 level, but I would feel better about this whole area if we had 500 or a thousand patients in each arm of a trial and we didn't see any of these real bad things. When people got endocarditis, it was

the usual flora that we were used to seeing. We didn't see an increase in resistance in the patients that had it or the time course of when they were getting it didn't shift.

That would give me a little bit more confidence that in fact, in trying to help people here, we are not, in fact, hurting people and creating a problem that in postmarketing studies may take a very long time to sort out.

DR. TRACY: I am just worried a lot about these numbers. If you have a 1.2 percent incidence of infection and you reduce it to .6 percent and of those .6 percent who get endocarditis, .1 percent, .01 percent have a poly-resistance organism. We are now setting the industry up to fail because you need tens of thousands of patients to come up with some type of analysis and you couldn't even prove with that teeny tiny number of extremely resistant organisms that it just didn't happen to be a bad day for that guy.

DR. DANNER: But you would protect against a bigger problem. In other words, if your numbers are correct, that is fine and that would suggest that the device is fairly safe, that you are not creating some bigger problem, but, you know, if the incidence of infection after putting in one of these valves is actually 2 or 3 percent, you have done a thousand patients in that arm and you have 30 or 40 people with endocarditis and you find of that 30 or 40 people, based both on historical controls and your

control arm in that study, that you are resistant Pseudomonas, candida, strange organisms that you are not -- you know, maybe staph epi(?) you don't see at all, but you see these other things. That would perhaps give you a little bit of confidence if you didn't see that problem anyway, that you are not missing a big issue.

DR. GILLIAM: But you are making it more difficult -- again, I think we have to go back to look -- if a company came up with a totally new valve and just opted for their sewing ring to have this antibiotic, you know, laden ring and made no claims to it, you know, they could certainly -- the way we are now get that through with our present criteria and what you are saying is on a factor of probably four to five times more difficult.

DR. DANNER: You know, that is exactly what I am saying, in fact, and I listened to your comments before very, very carefully and I think that what we are into with putting things in these cloths, we are into something that is, you know, just unstandard and it raises new safety issues that aren't raised by the other valves and which we have no experience with.

With these other valves and other materials that are used are thousands upon tens of thousands of experiences, at least empirically. With this, we are a little bit in a no man's land and I am not sure that it is

not correct to, in fact, ask for a better test.

DR. CURTIS: I don't think I agree with that. I mean, if you just look at it off hand, if you said a thousand patients in one arm and a thousand patients in another arm, you are talking about -- if there is no difference in the infection rate, 12 and 12, and then if you reduce that, you are getting down to 6 and 6. So, you are going to have to do 2,000 patients to compare 6 over here and 12 over here and look at what organisms there were. It is going to be hard to make any sense out of that anyway.

Brand new defibrillators, brand new pacemakers, brand new heart valves, I mean, they come to market after two or three hundred implants or something like that. Nobody has ever asked for 2,000 implants to be followed up in order to get something like that to market. So, this would be a burden that is well beyond anything we ask for a brand new technology, it seems to me.

DR. DANNER: You may actually get close to just being able to show efficacy, which has its own value. In other words, if you show that there is a 90 percent chance that this, in fact, is efficacious by running this trial with 2,000 patients, that has value because these devices are going to cost more when you put this stuff in them than they cost before. And do they do anything?

You have no idea. Also, by doing at least a

reasonably-sized trial, you will rule out any horrendous harm and that is important to know, too. What we are talking about here is very different than the devices that you are used to regulating here everyday. It is not the same thing. It is a different animal.

That is in part why you invited me and Dr. Reller here.

DR. GILLIAM: I think that, you know, the fact that it is new and different is quite honestly the very reason that this panel exists at all. I mean, I think almost everything that we bring before the panel is very new and different. I think that this is maybe something new and different in a new and different way, but it still --

[Laughter.]

I mean, when we look at our last valves that we looked -- I mean, we had a very similar debate and I think all of us can remember the -- wondering whether these newer valves without the sewing rings were equivalent to the ones who were not because they are manufactured in totally different ways.

So, I think the fact that this is new or not is -- this is what the panel exists for. But I do think that as Anne put it, I mean, to ask industry to do a study with, you know, several thousand patients, I mean, and we would ask every company to do the same for every valve and, you know,

I think that would be -- it would be absolutely wonderful from a scientific standpoint and I certainly don't want you to think that I wouldn't want to know the answer, but I think that we are probably not going to find efficacious -- that information, before something is in the market and probably in the market for a very long time.

DR. BRINKER: I think that one other issue that I think is of import is that the device issues, we have grown up over the years in a different kind of mindset than in pharmaceutical issues, where very often there is the wherewithal and the need to do large, vigorous clinical trials controlled in every way to find efficacy.

We have always for a lot of reasons been a lot less stringent in terms of devices for a lot of reasons. Now, you can argue that that is, perhaps, not as appropriate as in the pharmaceutical side of the regulatory spectrum, but the fact remains here that we are launched into a number of issues that reflect a device, not primarily pharmaceutical mode of therapy.

And that we have, I think, a little bit more leeway in determining even the necessity of demonstrating -- in fact, the demonstration of efficacy is not necessary if there is no claim to efficacy, which is something that I don't think that you would even think was true in the --

DR. DOMANSKI: Well, I guess, the question I have,

you know, this -- a lot of what -- although I don't buy into if there is no claim, it doesn't matter argument. I must say that, you know, we don't want to become unnecessarily burdensome, but I guess the concern that I have as I kind of listen to this -- and this is a bit out of my field -- but, Bob, I mean, are we -- I guess, I sort of hear the specter of some kind of a microbiological Pearl Harbor being raised, something we really didn't expect, you know. I mean, is that the specter that is being raised by this?

Otherwise, it seems burdensome to ask for a huge clinical trial and I, Lord knows, have spent years on this panel arguing for huge clinical trials, but I guess that is the question. I just don't know the answer to that. I mean, is there a concern that there is really something that we are going to find here that really is massive harm? Is there some reasonable possibility of that?

DR. DANNER: I think "massive" is not the right word, but I think there is a risk for harm and I think that though this is a device, what we are really being asked about today is a very unique way of delivering a pharmaceutical.

So, maybe the standards that this committee has normally operated under are not the right standards to apply. I am not saying that you have to then apply the standards of the pharmaceutical side, but perhaps some

compromise in between those. You know, I was throwing numbers out in terms of what we should do and I really don't know what those numbers should be.

I was also trying to get some idea of what size of study the industry would tolerate and still, perhaps, proceed. I don't know what those numbers are either. But I do kind of have the sense that this is not -- that perhaps the committee needs to think about shifting their paradigm a bit with this because it is a different issue.

DR. CURTIS: Susan.

DR. ALPERT: Yes. I would make two comments.

One is that one of the things that we are facing here, which we don't always face, is an attempt to make a superiority claim for a very small effect. We have told industry when they come and talk to us if your effect size is very small, in order to establish that with reliability takes a huge study. So, think carefully about what products you select because small effect sizes -- and we are talking here about going from 1.2 percent infection rate to something significantly less, even if it is half -- making those -- demonstrating those kinds of impacts are huge. It is not going from 10 percent to 5 percent. It is not going from 30 percent of showing an impact of 30 or 40 percent improvement.

We are talking about something very small. The

smaller the percent of that impact, the larger the trial in order to reliably demonstrate that. That is a fact. So, claims of superiority over the standard device requires a large study. That is the way it is in terms of really establishing the claim.

That is one thing I wanted to say. The second thing I wanted to say is that all products going to market need to be safe and effective for their intended uses as they are labeled. And whether the claim is there saying that it is an antibiotic that is intended to improve outcomes or not is very important.

And if you note for the device where a material change was made that incorporates silver, where the issue was an issue of data supporting the fact that the device remains safe and very careful wording about the fact that there is no impact, there is no data to say that this in any way improved clinical impact, was a combination of where we are with biomaterials issues and where the companies would like to go with claims issues. And we did take a mental cut.

We are asking for advice about did we step too far. How far can we step? And what are the risks of stepping? Again, silver posed a very different set of issues from a safety perspective for patients and they did test the impact on the performance of the product.

So, we have issue. We have started to step into this but we are now facing a different question. We have told those individuals, as well, any claim of superiority over a standard product needs to be supported with trials that we are talking about here. And whether we take a position ultimately that Dr. Danner talked about at what level do we expect that reliability, what percentage change with what reliability, whether it is 80 percent reliability and what statistical, those are issues that we can, in fact, discuss.

I am pleased to see that the panel has, in fact, brought all those issues to the table because that is why we are here. We are also, as was pointed out by Dr. Danner and Dr. Renner, we are talking about a pharmaceutical product type claim in a medical device and we do need to deal with the claim structure, again, not necessarily the -- we do have a different standard of demonstration of effectiveness. We have as our standard reasonable assurance of effectiveness and that is a different standard than the pharmaceutical standard, but we still have to meet our own standard.

DR. BRINKER: Susan, we need a little bit more guidance here because as I was speaking, I saw your head shake back and forth so vigorously that I was worried that we would need a seismograph.

One thing that bothers me is the differentiation between silver and antibiotics, not from pharmacologic aspects but from the regulatory aspects. Now, my understanding is that silver is incorporated without a claim to being protective against infection specifically. That is why they didn't have to prove this.

But the reality is it is incorporated because -- correct me if I am wrong -- because, gee, there was some animal data suggesting that there may be a decrease in infection and the only reason you would want this in it presumably is that maybe it does. It offers, perhaps, some value added at minimal or no risk.

If that is sort of the rational and you buy off on that, then the issue is -- and silver is -- because of the way it is being used, in my mind, it is a therapeutic agent. You can play the game but the reality for putting it in is because it delivers some sort of therapy, which might be effective. Because if you were sure that silver was entirely inert and didn't have any potential for an effect, there is no reason to put it in in the first place.

DR. ALPERT: Well, there are two issues. One is it is not therapeutic and I think that is very important. We are talking here at most about a material resistant to colonization, which has been established for silver not just in this setting, but in other medical device settings. So,

there is a history and there is an understanding and there is both laboratory and clinical and there is laboratory, clinical and animal data to demonstrate that silver does reduce colonization on a product, on a surface and that there is a benefit/risk thing that we also looked at in terms of whether there was any increased risk and that was, in fact, evaluated in a materials -- and impact on the reliability of the material, which was, again, something that as Tom pointed out, we do as materials change.

So, we dealt with it as a materials change and we did ask the question as to whether there was any issue and we very clearly again -- and we are talking about this because this is a continuum. There is no question about the fact that this is a continuum, that we are moving along a continuum and that we have to put -- we have to figure out as we step into that continuum what the appropriate kinds of questions are.

We asked the question as to whether there was an introduction of any risk to patients. We couldn't find any risk that was introduced. We have been talking here about low risk being introduced by other types of additives to these valves and by anti-infectives that are either used in therapy or that have an impact on selection of bacteria within a given patient.

Those are risks that we need to address --

DR. BRINKER: That should help clarify our thinking because by that -- from what I am hearing is that the main issue still is not necessarily an efficacy claim but an exclusion of risk -- I know you are doing this but --

DR. ALPERT: It is a little bit of both, Jeff. It is not so simple. As I said, we are on a continuum. I mean, it is clear that there is concern and you raised the concern about implied claim, which is why we put wording in to say there is no clinical data on this product that says that this, in fact, decreases infection rates. And that is very important. That is one of the -- but making further claims than that, we hope that that will communicate to the community, to the clinicians using the product, that there has been no demonstration that, in fact, there is a specific benefit to patients.

As Tom pointed out, FDAMA did tell us we pay attention to what is in the label and if we believe that what is in the label poses a risk of off-label claim or use, implied claim or use, which is that this would be therapeutic, to quote your word, we put in the wording that said this is not therapeutic. This is not clinically established. This is simply the material and the issue that has been established in the lab, but there is no clinical information to support any change in behavior.

What we are talking about trying to do here with

the introduction of antimicrobials into rings is, in fact, to change both patient outcome and behavior and the way in which the valves get used and those take data, clinical data.

DR. BRINKER: I mean, I really have to think about how -- the way in which the valves get used are going to be altered by the incorporation of this device as opposed to silver, for instance, and I -- I agree that in my eye, based on what has already been approved, the issue is what is special about antibiotics, as opposed to an antiseptic, if you will, and I think there are differences.

Therefore, I think we should focus on those differences primarily rather than to sort of -- since you have already set the stage for this, continuum or no continuum, the issue is that it is going to be hard put to look at this in any other way, except that there is a difference between antibiotics and antiseptics and we have to set a criteria by which to examine what are the differences, what are the potential risks of one as opposed to another and what should be the scale upon which we evaluate those particular risks of antimicrobials, especially since that one could conceivably make the claim, as was made previously in the central venous catheters that such an antimicrobial -- an antibiotic incorporation into the device itself might decrease colonization and you might

say, well, this is basically -- we are not making an infection claim, but we know we can show decreased colonization in the animal with this mixture and that is the same as the silver business. So, the only thing we are going to say is there is no clinical benefit to putting in an antibiotic but in animal studies, it decreased colonization or something like that.

DR. DOMANSKI: Susan, isn't that different, though? I mean, in the one case you have a biomaterial that is resistant to colonization. In the other case, you are delivering a drug systemically. I mean, I don't see -- you know, this is way down the continuum. I mean, it almost is a discontinuity --

DR. BRINKER: I don't think -- the idea of incorporating a low -- the kind of antibiotic that we have seen is not a systemic effect and let me ask, just as an aside, is there any detection of any silver leaching? Is that possible? Has somebody looked at minute levels of silver to say that that there is no --

DR. ALPERT: I don't know the answer to the question but the folks -- if the issue -- as I said, there is animal work and there is also clinical experience with materials impregnated with silver that did not raise those issues. And that is the basis on which we made -- if you are telling us we made a mistake, then, you know, that is

appropriate if that is what you believe to tell us that.

DR. BRINKER: I would never say that.

DR. ALPERT: Perfection is not our middle name. We do the best we can with what we have. We try to make appropriate decisions with the best science that we currently have on the table. That doesn't mean it is perfect.

DR. HOPKINS: I think even in our packet there is a study by Tweeden(?) that you included in the packet that did do cell toxicity studies on the silver, which supports their use in this application.

Not to beat a dead horse again, but I really think that there is -- there is some justification for raising the bar as we move along -- this is maybe not a perfect continuum. It is sort of a stair step and that is a disinfectant or an antiseptic like silver in a mechanical prosthesis, I think, has been appropriately managed by the decisions that have been made, based upon the animal data that is available and the history of its use in humans. It goes back really years and years for gonococcal infections, et cetera.

The next step of incorporating such an antiseptic into a biological prosthesis clearly mandates some sort of long term follow-up on the effect on durability. I mean, that clearly is another order of issue. Then going into a

new drug delivery system, even if it is a local drug delivery system, that raises the bar again and I think that maybe as we get into the afternoon, we are going to be talking about exactly what that bar should be.

I have a very easy time kind of conceptualizing the first two and I think we have thrown out some possibilities of exactly how you design that in a pretty cost efficient way for the industry. But this is a drug delivery system. If it reduces the use of vancomycin indiscriminately intravenously by cardiac surgeons in the country or vascular, it will have a beneficial effect.

But those are all might be's. I mean, I think there is going to have to be a higher bar for this type of a drug delivery system.

DR. CURTIS: Okay.

I will let you make your comment before --

DR. DAROUICHE: Thank you.

I believe there are several issues on the table and I am just going to try to help you out with some of them. Again, I do not dare to differ with the FDA. However, sometimes I would beg to offer a different opinion.

My colleagues -- actually, I am going to ask the expertise of my infectious disease colleagues, Dr. Reller and Dr. Danner.

The last time I checked in the books, microbes are

a group of organisms that can be either bacteria, viruses, fungi or parasites.

So, in order for us to understand that a certain antiseptic agent, as in silver, is an antibacterial but is not an antimicrobial, I really do not understand that. Maybe you can help me understand that.

Second, and I really understand the concerns of Dr. Danner about preventing super infection with the use of antimicrobial coated medical devices. And actually we have looked at that. We have actually conducted two randomized prospective clinical trials.

In the first one we compared antibiotic coated central venous catheters with uncoated and the second trial, we compared antibiotic coated catheters with antiseptic coated catheters and we collected every single organism that was cultured from the catheters. And the distribution of organisms was essentially the same and the antibiotic coated and the antiseptic coated and the uncoated arm. The reason for that is very clear because the two companies there decided to do those studies, which eventually led to 510(k) approval by the FDA, were wide enough to use combination of agents that have broad spectrum antimicrobial activities.

We did not end up with any super infection by candida nor did we end up with any super infection by gram negative resistant bacteria. And that is very different

than using a single agent for prevention of infection as we are doing now, heart valves and vancomycin. And, in fact, it may even be better than coating heart valves of a single agent if that agent is truly an antibacterial and has no other antimicrobial properties.

Now, having said that, it is always important to understand that, yes, we are talking about rates of infection of endocarditis being very low, 1.2 percent in the first year, but for clinicians ourselves, if I have my father or my mother, who is embarking on a heart valve surgery and I know there is a product that may be helpful -- I am not sure it is definitely helpful, that may be helpful, you bet you, I am going to use that.

Therefore, I think the only reason we were able to do those prospective, randomized studies for central venous catheter was because it was feasible. All we needed was 298 patients in one study and we needed 405 patients in other studies. The median duration of catheterization was seven days as opposed to heart valve, which may be one or two or three years for a study.

So, I really would like you to think about that before you make your conclusions.

DR. CURTIS: Thank you.

I think we should adjourn for lunch and meet back here at 1 o'clock.

[Whereupon, at 12:10 p.m., the meeting was recessed, to reconvene at 1:10 p.m., the same afternoon, Tuesday, June 30, 1998.]

A F T E R N O O N S E S S I O N [1:10 p.m.]

DR. CURTIS: We are going to get started.

Question 4 is the one we are addressing first, which actually has 25 sub-questions to it. So, I hope we go a little faster than this morning.

Question 4 overall says: Do the following questions represent all the issues, which should be considered in addressing the safety and effectiveness of these products? If not, what other questions should be addressed?

They are grouped here. The first section of questions relates to issues related to antimicrobial section. Do you have all of these separately, the questions?

(a) What is the purpose of the antimicrobial? Is it intended to prevent the colonization of bacteria on the product?

If some of these are short or easy answers, I think that would be helpful. That will give us time to concentrate on some of the more complicated ones, which I think come up near the end.

What is the purpose of the antimicrobial? Is it to prevent colonization? Is that all we are looking for?

DR. GILLIAM: I think that sort of device and maybe -- I think a lot of these questions, I am concerned

since we don't have a device in front of us, that we could spend a lot of time talking about, you know, various purposes of an antimicrobial, but they may change depending on the device and the different antibiotic, I guess, if that is used at the time. So, I am not sure that we can answer that question.

DR. CURTIS: Well, the purpose of the antimicrobial is first to prevent colonization and then as a result is to prevent infection. I mean, that is what we are looking for.

DR. GILLIAM: Yes.

DR. FERGUSON: I would vote "yes" on that.

DR. SETHI: Yes.

DR. DURACK: Just a brief comment on that. David Durack. I am representing IDSA, but I also work for Bacon, Beaconson(?) and we make devices, but not in this field.

Strictly speaking, the intention is to prevent infection, which could be either by preventing colonization or by eradicating organisms shortly after they colonize. We learned this from the prevention -- early prevention studies using foreign materials.

It is possible to prevent an infection by having colonization followed by eradication. So, either one. I mean, it is a matter of definition.

DR. CURTIS: Did you want to make any other

comments, you know, because we are not going to have like another formal public session and you had asked a chance to speak.

DR. DURACK: I never refused a moment to say something.

Just with regard to the discussion this morning about the super organisms, I loved the comment about the specter of microbial Pearl Harbor. I think we should just analyze that a little bit further. It is possible to increase the proportion of resistant organisms without actually increasing the total number.

So, just to take an example, if you had a hundred infections, 90 are caused by common staph, et cetera, and 10 by bad organisms. You raised the example of candida. If you had an intervention that brought the number down to 20 by getting rid of most of the common organisms, you would have 50 percent candida left. You might say you had created a problem, but actually what you have done is prevent 80 infections. So, I would just raise the issue that there is a difference between promoting resistant organisms and just raising the proportion that you are dealing with.

I think that is something that the committee should consider. It is perfectly good to prevent 80 infections even if you are left with 10 candida if they are the same 10 that you would have had anyway.

It is, of course, theoretically possible that you might promote or select resistant organisms, microbial Pearl Harbor, but more likely than not, you would prevent some and be left with the residual ones that you would have had anyway. I just wanted to throw that in.

One other thought, I would like to give an opinion about vancomycin, which is, to echo something that both of our other experts said, I think on -- I represent the IDSA, but this is my opinion. I think it would be shared by many other members of the IDSA. I would like to say not only no promotion of vancomycin as an incorporated antibiotic, but actually something to go against the use of vancomycin.

Of course, it is a candidate, but everything we know is that they have vancomycin in the environment, in the operating room, in the patient, is a problem today. So, if the committee sees fit, maybe there should be some ranking of antibiotics that would be less desirable to have in the -- if it is decided to incorporate them.

DR. CURTIS: Okay. I think that would naturally lead into the next question, which is: (b) On what basis do you select a particular drug for the treatment as organisms vary considerably?

How would drugs be selected for this? I think either Dr. Reller or Dr. Danner might want to comment on this. I think you made some comments this morning that

relate to this. You were concerned about any of the antibiotics.

DR. RELLER: Well, some of the ones that have already mentioned, all of the data support that today's current state or the gram positive organisms, the culprit, there are pathophysiologic regions for that; epidermitis or coagulase(?) negative staph aureus, and increasingly now enterococci.

I said there are two aspects of selection of antibiotics. The first principle is not anything that would be used and vancomycin, gentamicin, rifampin are anchors in the therapy of prosthetic valve endocarditis.

Then the other side of that is of the most likely organisms, the most difficult organisms in this devastating, though, relatively infrequent infection, are the other candidates effective, intrinsically infective, active, against these organisms. Many of them are not and it brings me back to where we were earlier this morning; that is, the issue of efficacy in addition to safety.

Just before lunch, Dr. Alpert raised and asked for an honest assessment. You know, has the Agency gone too far and where to stop in terms of incorporation of compounds into these devices? I think the place to stop and require something fundamentally different in terms of assuring safety, and I think, as well, of some measure of efficacy is

with the incorporation of antibiotics into these devices.

DR. CURTIS: I think the issue about how do you sort the particular drug, a couple of the issues would be you don't want to use one that is used commonly for treatment because you don't want to have that be the thing you use, but it has to be active. It is going to be the primary pathogens of concern, which is one of the other questions in here.

But, as you said, you know, early on, staph aureus, staph epidermis, late, the strep species, that sort of thing, for which we are going after. So, you want drugs that have activity against them but are not the most common ones. I think that is something that could be worked out.

You cannot use a drug that is going to be effective for everything that could possibly infect a valve or a graft or whatever. You have to go after the most common pathogens.

Are there any other comments on that?

DR. RELLER: I would like to -- it would be easier to render comments perhaps about particular antibiotics mechanisms of resistance known propensity for developing resistance on exposure to agent. I mean, there are things known about all of those questions. As now, any of the manufacturers, device makers want to put forth some of the agents that have been proposed. Maybe it would elicit

response from the committee and consultants as to what their thoughts about the agents are.

DR. CURTIS: I think the next three parts to this issue are all somewhat related and don't necessarily have to be discussed separately: Is the drug bactericidal? What are the primary pathogens of concern, we just mentioned briefly. Is there a known resistance pattern to the drug?

These are all issues related to antimicrobial selection. Is there anything that we know about development of resistance patterns or types of antibiotics that should be avoided? It sounds like a combination of two, from what I heard this morning, would be superior to using a single antibiotic. I don't know if you have any comments on that.

As I said, the primary pathogens of concern are usually known. I mean, usually the ones that are most commonly caused -- especially early infection. If you are talking about a heart valve, that is -- since endothelialization may render -- there wouldn't be any late effects with use of antibiotics. You are looking at early infection. You want the hippapathogens(?) that are most likely to cause early infection. The drugs have to be bactericidal or bacteriostatic.

DR. TRACY: What antibiotics are on the catheter, the Swann-Gant catheter? Does anybody know?

DR. DAROUICHE: It is the combination -- it is an

antibiotic combination of menofaxan(?), drisantan(?) and antiseptic combination of chlorhexidine(?) and silver sulfadiazine.

DR. TRACY: So, a bit of everything.

DR. CURTIS: Why were they selected?

DR. DAROUICHE: They were selected for several reasons. First is that the combination of the two agents in each case actually has some logistic in vitro activity.

Second, at least for the antibiotics, I can tell you that they chosen because of different mechanisms of activity. Rifampin acts by inhibiting DNA dependent RNA polymerase, while menofaxan acts by inhibiting protein synthesis and, therefore, it is unlikely to have a single bacterial mutant that may develop resistance to both drugs where there are two different mechanisms of action.

Now, mind you that these two agents were also selected wisely because neither of these two agents share the same mechanism of action as vancomycin does, which we know acts by inhibition of cell wall synthesis. So, even if these were agents that were to be used for coating and that coating failed to prevent infection, it really would have not only this clinical impact on the patient because the patient can still receive vancomycin.

The third reason this combination was used because these two agents are lipophilic. So, they are always

together. They don't leach one at a time and the other followed by that. So, that is why they are always together on the catheter and once you stop detecting one, you will stop detecting the other. These are really the three main reasons this combination of antibiotics was selected.

The reason the antiseptic combination was selected is because, in fact, silver is a meek antibacterial agent and chlorhexidine is a more powerful antimicrobial agent and the combination was shown to be in vitro to be synergistic. However, I would remind you that even the terminology that we use in the medical literature of antiseptic combination of chlorhexidine and silver sulfadiazine, in fact, is not a hundred percent, too, because we all know that silver sulfadiazine has a sulfa component and that sulfa component is considered by many authorities as being an antibiotic.

So, that is why it is really important to know what agents we are dealing with, rather than try to say, okay, this is an antibiotic. This is an antiseptic. This is antibacterial. This is antimicrobial. We really have to talk about specific combinations of agents.

DR. CURTIS: I think that is a very rational approach to those questions and that sort of approach would have to be used in developing anything else that was new.

Any other comments on those?

DR. FERGUSON: I am still unclear as to whether we

are talking about a combination of antibiotic and an antimicrobial that would be presented by one company. Another company would be presenting two antibiotics; another one different antibiotics.

Is there any reason or rationale to selecting combinations and the companies agreeing sort of that those would be the ones that would be used or is that way out of sight?

PARTICIPANT: Well, we are not prepared today to put in a public forum what we are considering.

DR. FERGUSON: Okay.

DR. TRACY: I think the question about what pathogens that is one or two questions down, what pathogens are involved, I think that is important in answering the questions. The one reference that we have suggests that 10 to 12 percent are caused by fungi of early endocarditis. So, it does seem that having not only an antibacterial agent present would be helpful.

So, I think -- I don't know that we are really in a position to answer these questions specifically, but I think we have to review carefully what the organisms are. We just have this one reference, as far as I can see that details the common pathogens. But I think a lot of the answers will depend on what actually is present in the community.

DR. CURTIS: Other comments?

DR. HOPKINS: I think it is a little card to respond in the absence of specific proposals because I think you can even flip this entirely around and then maybe what should be incorporated are if you are going to go down the antibiotic road, you should be incorporating antibiotics that are aimed at the most severe infections because I would much rather deal with a strep verdans post valve implant bacterial endocarditis any day.

So, maybe what should be incorporated are anti-fungals and anti -- aimed at not the most common bacterial endocarditis pathogens, but the bad ones. So, I think there is a whole bunch of different strategies that could be worked out and I think the panel is kind of working in a vacuum as we try to sort through them and all the potential variations.

My answer to most of these questions is "yes," they have to be addressed.

DR. SETHI: And the pathogens change over a period of time. You know, as new antibiotics come up, we have seen the pathogens. I think, at least from a personal experience, 10 to 15 percent fungal infection maybe is too high, but, you know, there are the data, which was all the data. We don't see that much fungal infections anymore because we are not using antibiotics for as long a period of

time as we used to use, say, 15 years ago.

This is an ever-changing field at this point and to make a specific recommendation is probably not right at this point.

DR. CURTIS: I am not sure that many of these questions -- I don't really think that many of them were designed for an answer that we are supposed to say what the answer to this is, as much as are these the sorts of things that a company is going to be able to answer or know the answers to in designing their product so that all of the information on safety and effectiveness will become available. So, in that case then, they would need to say what are the primary pathogens of concern. They wouldn't need to say is there a known resistance pattern to the drugs that you are incorporating into your product and that sort of thing.

DR. HOPKINS: And they would have to deal with dose release issues. What are they trying to achieve?

DR. CALLAHAN: I think that is the idea of the questions is to just get that general response. But as you get towards the end of the questions on 4, (m), (n) and (o) are a little specific in terms of trying to elicit is there a way of getting at risks, what are the risks.

DR. CURTIS: Okay. In which case then I will -- we will spend a little bit less time on the next few

questions because I think they do get a little bit more complicated as we get down.

Any other comments on the issues we just covered?

If not, let's move on to the dose release issues. The first one, (f), how is the drug applied to the product? Is it impregnated into or coated onto the product? You know, I am sure there is any way any of us would have any reason right now to say one is better than the other. I mean, you have to know what the answer to that is. You have to design it into your product and then you have to test it. Right?

Any comments on that?

(g) Is the amount of antibiotic impregnated into or coated on the product sufficient to produce a local effect for the time required to prevent colonization? I think you need to know the answer to that. Right? That is an important issue.

Okay. (h) What is the dose/duration effect of the drug? We would want to know the answer to that. How long does the effect last? Is it hours, days, weeks? How long? That would be something that would be done from in vitro studies.

(i) -- and if anybody wants to say anything, just speak up.

DR. HOPKINS: I think you are also looking at

penetration. Not only what is the dose in terms of time effect, but what is the dose in terms of space effect or how far is it penetrating? What is the local -- what is the actual space of the local effect?

DR. CURTIS: Good point.

(i) Is the dose duration effect adequate for potentially affecting the incidence of infection? That is a good question. It sounds like a space effect again.

DR. GILLIAM: They certainly should know that when -- depending on a specific product, when they come to market, they should certainly know the answer to that question.

DR. CURTIS: Okay.

(j) Will the drug dissipate before the product has time to endothelialize? Obviously, if all the drug leaches out in the first 48 hours and you don't endothelialize for six weeks, that would be a problem. So, that would be something that would be important to know and should be answerable with preclinical studies.

DR. GILLIAM: And that doesn't imply either good or bad, does it?

DR. CURTIS: No. That is right. Just is it there.

DR. SETHI: The other thing will be the shelf life of the drug, which is being used, you know, and how good

that drug will be. To put the antibiotic in the valve today, is it good four years from now? Because, you know, it may take that long for the valve to get implanted. So, I think that should be somehow reflected in here.

DR. CURTIS: All right. It doesn't do any good to have ineffective drug eluting out --

DR. SETHI: That is right, yes.

DR. CURTIS: -- six weeks down the road.

(k) What type of elution study will simulate the proper flow conditions? Which solution best simulates blood in terms of leaching and diffusion of an antimicrobial? I haven't got the foggiest idea what the answer to that is, but if you are going to design preclinical studies, you would have to know. I don't know if there any models even for that.

No volunteers. Go ahead.

DR. RELLER: To me, all these questions that could be addressed experimentally are important in selecting a potentially effective product and might be useful in that way, but at the end of the day, only demonstrating effectiveness will do the job. I think it is important not to consider these as surrogates for demonstrated effectiveness.

DR. CURTIS: I think that is true, but I don't think any -- I mean, preclinical studies are designed to

answer these sorts of issues before you get to the study that gives you that clinical answer.

All right. Preclinical test issues. In (l) we have how long does it take the product to endothelialize? Again, I think an important question.

(m) How great is the possibility of occurrence of inadequate endothelialization associated with drug resistant organisms?

DR. GILLIAM: That might be an extremely difficult, you know, question to answer, at least in humans. I would defer to the infectious disease folks. Do you think this is something we could adequately expect them to have an answer to coming to -- this is preclinical. Would that presuppose that the same pathogens exist in a preclinical model? Do you see where I am headed with it or maybe I am just totally ignorant of this whole question.

I read the question as saying that, you know, there may be drug resistant organisms that may have an effect and if it is preclinical, we don't have enough data from humans to say that.

DR. CURTIS: Well, I am not sure if it is all the same question. I mean, inadequate endothelialization could be something that comes about because of the way the product is designed. It doesn't promote endothelialization like you would normally expect. Lack of endothelialization could

allow other organisms to get in there. I am not sure --

DR. FERGUSON: I read it as an association. Is it not saying --

DR. CURTIS: It says "association," but I am not sure --

DR. FERGUSON: Well, I mean, doesn't it say the drug resistant organisms can be the cause of inadequate endothelialization?

DR. SETHI: That is the way I read it also.

DR. GILLIAM: That is how I read it, not just the fact that there were drug resistant organisms in the body, as well as inadequate endothelialization. I somehow assumed the two were related and the question -- maybe that wasn't the intent.

DR. CURTIS: How would you test for that?

DR. GILLIAM: That is why I brought it up. I don't have the first idea how you would test for it. I thought this was coming under preclinical.

DR. CURTIS: Right. I think it is a rational concern. I have no idea how you would test for it, though.

DR. HOPKINS: As I look at (l), (m) and (o), I think it is going to be very difficult to create good studies. Endothelialization is variable anyway. We know in the vascular grafts, it is a certain distance down the graft. It is certainly not the whole graft.

Endothelialization may, in fact, be not the right term because much of this is pseudo entema, not true entema, not true endothelialization. This is going to be very, very difficult to create a study. And, in fact, most of the models, the animal models, with which I am familiar, have a variable parallel to the human situation.

Some of the animals have very exuberant pannus formation. Others don't. All the ruminants have continuous bacteremias. So that there are some good models that can be done, but -- that can ask the question whether these can prevent or postpone infection for a period of time, but I don't know if you are going to be able to grade endothelialization. I am not aware of a good model.

DR. CURTIS: Okay. And (n), it says how strong is the evidence that the duration and intensity of treatment will prevent development of resistant organisms? I am not sure I really follow that one either. It seems to me that long intense treatment would promote development of resistant organisms or that would be at least a concern that that might happen.

How strong is the evidence? I think you were getting at that, Rick, about how do you get a model of that to learn the answer preclinically. I don't know that you could do that either.

Any other comments?

(o), that is somewhat related. What is the risk of an allergic response, possibility of renal damage, et cetera?

DR. DOMANSKI: Well, they are using well-defined antibiotics where those numbers are much a part of the literature. I am not sure why one would ask them to try to gather separate data when those data are already out there.

DR. CURTIS: These are not systemic antibiotics, where impregnated levels are going to be low or undetectible, except near the actual device itself. I would think that the risk of an allergic reaction or other bad reactions should be lower than it would be with systemic use of any one of these drugs.

DR. DOMANSKI: Well, whether -- it is certainly not higher.

DR. CURTIS: It is certainly not higher.

DR. DOMANSKI: The upper bound is pretty clearly defined in the literature already.

DR. CURTIS: So, in your mind, it would not require any other specific --

DR. DOMANSKI: Gee, I wouldn't think so.

DR. CURTIS: I wouldn't think so either.

DR. DOMANSKI: Because some of these things would be pretty knotty little things to try and collect, to try to demonstrate that you had really adequately done it and it is

stuff that is probably not too important.

DR. CURTIS: Okay.

(p) Is there a possibility that the antimicrobial treatment will kill tissue as well as pathogens? That is an interesting question.

DR. DOMANSKI: I don't understand that one either because the effect on tissue of those antibiotics is pretty well-known. I mean, it is not -- this isn't news.

DR. CURTIS: I suppose the concern may be a very high level in a very localized area like that, but regardless if you have animal models and you are implanting these valves and you are looking at it, you ought to be able to see if there is any tissue damage at that point.

DR. SIMMONS: And that may be all they are saying is that you should have cross sectional animal studies done to make sure there isn't tissue necrosis.

DR. CURTIS: Right. It seems like there could be a theoretical possibility and it is easy enough to answer that particular question even if some of the previous ones are a little bit hard to get at.

DR. SETHI: Can I just make a comment about coating of the silver, which is bothering me a little bit about -- for some time now. Though the FDA has approved -- has given their blessing to use silver on these valves, but silver does cause a lot of reaction to the tissue and animal

data, which we have seen, is pretty short term data. This silver coated valve that we did for a long time, with the impression that you will protect this child from endocarditis, but we have shown the -- I think it is too early at this point to say that silver is not harmful.

The second thing is it implies to me when a product comes to me, when the men come to my office and say there are two valves. One will last 20 years, a new improved valve with silver coating on it. It implies to me it is a better valve. Though he may not say in those terms, but to average person, to average physician, to average cardiologist, it implies that it is a better valve.

How are we going to at this point tamper with the enthusiasm, which our cardiologists have got right now. If this is a new valve, we should put in the patient because it is supposed to have less endocarditis incidence.

DR. CURTIS: I think that gets back to an entirely different issue, which is labeling and --

DR. SETHI: -- to the discussion sometime because I will be leaving a bit earlier and if it isn't somewhere in the bottom part of the discussion, it will come up again.

DR. CURTIS: Okay.

DR. SETHI: I think this issue really is -- you know, instead of antimicrobial, you can use antiseptic treatment. You can change the wording there if there is a

possibility that antiseptic -- I don't think it will cause the reaction. In the same kind of way thinking, going through my mind when I look at this question.

DR. CURTIS: Sure.

DR. SETHI: Thank you.

DR. CURTIS: I guess that leads into (q). Does the application of an antimicrobial pose potential long term effects on the product? I think we actually discussed this quite extensively this morning, concerns about how the valve would hold up and that that would have to be looked at formally and I don't think we need to go back over this. I think we did cover this.

(r) Does the antimicrobial pose potential thrombogenicity concerns? If so, how should this concern be addressed?

I think we were talking about premarket studies or looking at how the valve holds up. I think thrombosis is one of the normal complications of -- after valve surgery that one would look at and we wanted to be sure that it was no higher than expected for any other marketed valve. I think that also is something that we have covered.

Does anybody have any other comments?

[There was no response.]

All right. (s) is an interesting one. What effects, if any, does the sterilization process, steam,

ethylene oxide, irradiation, and device aging have on the activity levels of the antimicrobial? That is extremely important. It won't do any good to have an antimicrobial implanted and then sterilize the valve when it is all gone. So, it is a fundamental issue that has to be answered and that would be answered in preclinical testing.

(t) is a long one. How would the usefulness of animal data be characterized in demonstrating the safety and effectiveness for the proposed human use? What animal model is most appropriate? Should the animals be anticoagulated or not? Should prophylactic antibiotic be used before and after surgery? At what time intervals should be observed? How many treated and how many control valves need to be implanted to assure that there is enough data to answer the questions? How will the pharmacokinetics of the antibiotic treatment be assessed?

So, this is basically a question as to how to design animal studies for this -- for these products.

DR. TRACY: I guess the important thing is to think if there are any other issues that need to be addressed in an animal study, rather than us trying to come up with specific answers to these things you have read. I have no clue. Probably Rick does, but I wonder if anybody else has any -- are there any other issues that need to be addressed on the animal model?

DR. HOPKINS: I think you are exactly right. As you design and start doing pilot studies, you are going to find a lot of issues that have to be resolved. I think the point is that a good chronic implant animal study should be done and that should be a component of the preclinical studies. There are a number of models out there; the juvenile sheep model. I can tell you from personal experience that if you don't anticoagulate and you don't keep on antibiotics, they will get infected. So, it is a great model to show positive results if they are going to be shown.

Dogs are pretty similar. They will get infected eventually. So, there are good animal models out there that could be done with and without anticoagulation. I think as was mentioned this morning, there are a couple of different pathophysiologies that occur. One, of course, is infection of the ring itself, blood borne pathogens.

And the other is where clots form and, in fact, bacteria seed onto the clots and you get endocarditis in that fashion. So, I think the key is that at least the juvenile sheet, chronic implant model, should be used. Perhaps other models could be designed but they should be chronic models that test the various components. Certainly 20 weeks would probably be the minimum.

DR. CURTIS: That issue --

DR. DANNER: In animal models, what organisms are involved?

DR. HOPKINS: Oh, just --

DR. DANNER: Because you were talking about them getting a spontaneous --

DR. HOPKINS: As I recall, it is gram positives mostly, but they cause really big vegetations, which end up occluding the valve. But we were looking at it for other reasons. So, we didn't culture them out. But as I recall on the photomicrografts, they were mostly gram positives.

DR. DANNER: And, clearly, you could do sub-routines of this. You could inoculate the animals, as has been done in various kinds of vascular graft studies, where the animal gets inoculated with staff or strep or what have you. So, there is a series of these that you could do, but in addition to the acute studies, where you are inoculating the animal, you really need to do some chronic studies, where you have autoinoculations, to really see what the chronic effects are.

DR. CURTIS: One of the things -- you know, it depends a little bit on what you are trying to answer. If you would like to get at at least in animal studies whether the antibiotic decreases infection, I think you would like to do the studies without prophylactic antibiotics; you know, increase your chances that you are going to have an

infection occur. Maybe that involves not using any anticoagulation as well.

Give yourself a worse case scenario and have some animals implanted with a valve with the antibiotic and without the antibiotic.

DR. HOPKINS: Well, I can tell you in the sheep, if you use perioperative antibiotics and perioperative anticoagulation and then stop them at day three, send them out to the farm and you bring them back, most of them are infected in like 20 weeks.

DR. SETHI: Without anticoagulation, they all get clotted.

DR. CURTIS: So, you would have to use anticoagulation but don't use systemic antibiotics maybe.

DR. SETHI: I don't recall what protocol we have used, but I know that we did some work with anticoagulation and they all recovered very fast. So, we feel that anticoagulation is important.

DR. CURTIS: You said they all get infected.

DR. HOPKINS: If you leave them long enough they will get infected.

DR. CURTIS: So, you would need small numbers then, you are saying?

DR. HOPKINS: No, I think it is a good model.

DR. CURTIS: So, a relatively small number of

animals would be necessary in order to show whether there was an affect on infection rate.

DR. HOPKINS: In the chronic models. In the acute model, where you are doing an inoculum acutely to see on day one -- I could envision a study where you gave a series of doses and there are lots of studies in the literature, which are -- microbiology guys probably know, but there are dose response curves to infecting foreign bodies in the vascular system. Those could easily be done, as well.

DR. DANNER: When the animals get infected, do they have one organism on the valve or is it multiple organisms?

DR. HOPKINS: You are really stretching my knowledge because the studies where we got infected sheep valves were really aimed at other things. I can't answer that.

DR. DANNER: I mean, it seems you could answer the question if the valve was selecting out a different type of organism, sort of a variation of the issue Dr. Durack brought up again, but whether it -- you know, it just reduces some and leaves the residual or whether it actually alters the flora that ultimately sticks to the valve and causes an infection. It seems you would need some kind of -- you would need models that used polymicrobial challenges to see if an impregnated valve versus a non-impregnated

valve picked up different organisms from the same challenge.

DR. HOPKINS: Your control arm where you didn't have anything would help you with that.

DR. CURTIS: I think, too, though, if you wanted to look at how the valves held up and you had chronic studies for that, you would have to study animals where you are not trying to get infection, where you are trying to give them the best treatment possible because you are going to want to look at the pathology of the valve at explant and see that you didn't have excessive pannus formation and all the negative things that we are concerned about.

So, there have to be studies along those lines.

Other comments on this question?

[There was no response.]

All right. Then let's move on to the clinical issues. (u) In the long term, what other clinical benefits, for example, better endothelialization, are expected from the treatment? I don't think I would expect any, aside from, hopefully, lowering infection risk.

DR. HOPKINS: Well, except in the silver data, you do get better -- you get a thinner pannus.

DR. CURTIS: Thinner pannus. Okay.

DR. HOPKINS: Which armchair-wise means there is less distance for blood serum level of antibiotic to penetrate in terms of preventing or treating infection. So,

you may have -- once again, this may be an area where you get unexpected results.

DR. FERGUSON: [Comment off microphone.]

DR. CURTIS: (v) Should the patient be treated with prophylactic antibiotics prior to and following the implantation of the valve?

DR. SETHI: I would say "yes." I think that the motive to give antibiotic just -- more than just to prevent endocarditis of the valve. There is no clearcut randomized data to support what I am saying, but the fact is that we give antibiotics to all the patients undergoing cardiac surgery and this is prevent many problems.

DR. CURTIS: I think, too, to go from a situation where we are swishing valves in antibiotic solutions and giving all these intravenous antibiotics and saying don't worry about it. Just take this valve. It has got the stuff impregnated in it and you will be fine. It would be hard to convince, I think, a lot of surgeons to do that.

DR. SETHI: I think it will be hard to convince most of them, if not all of them.

DR. CURTIS: Right.

Is there a general consensus that systemic antibiotics should be used? Okay. A lot of nodding of heads.

(w) What improvement is anticipated in the

infection rate? Is the antimicrobial intended to affect the early onset of infection?

DR. GILLIAM: I don't think we have -- I think they may have a good guess when they come to the clinical issues, you know, the company, but I don't think we can have an idea without knowing an antibiotic that they would use. Maybe their preclinical studies can give them a hint as to what they can look for, but I think that is important information to start to consider, particularly after you do the postmarket studies.

DR. CURTIS: Well, I mean, if an antimicrobial were not intended to fight infection, I don't know why we would be using it. So, that would have to be the intent of it.

Improvement in the infection rate, you know, how much improvement is worthwhile to go through the testing and developing the product and then using it in people and --

DR. HOPKINS: Well, Dr. Naftel addressed that, I think, to reduce from 1.2 percent to 0.6 percent, to reduce by 50 percent reduction in incidence, he predicted what, 4,122 patients would have to be entered into the trial.

DR. CURTIS: You know, just sort of -- you could say any improvement is fine and any improvement is fine as long as you don't bring out these resistant organisms and if you just change the ratio as Dr. Durack was saying because

you have eliminated some of the common ones. That is okay, too.

In terms of proving things, you know, trying to prove a 30 percent in infection rate here, which is the sort of goals a lot of times we are looking for in clinical trials, minimum 20 percent, 20 to 30 percent often aimed for, would require an extremely large trial here to prove that. So, that would be difficult.

(x) Should antibiotic treated devices be placed in every candidate prior to testing it in high risk patients; for example, history of infection, patients with infected devices, drug abuse, immunocompromised patients, et cetera?

DR. GILLIAM: I think we talked about this earlier.

DR. CURTIS: It would be extremely difficult to go tease out those few patients, who would fit that category. So, it would not really be feasible to do it that way. So, we would say "yes," you would be placing it in every candidate.

(y) What information needs to be provided in the device labeling to assure that the physician has sufficient information to make appropriate decisions?

I think we were covering that, too, as we were talking about the fact that we are not going to be able to

make any claims that haven't been proven. And we are going to look at safety and that -- we might be able to get at things like lower colonization rates, but that you wouldn't be able to make a claim about reducing risk of infection until that were proven and also, I think, we might want to add allergy data, you know, this specific drug, its potential for reactions. That may be something separate, other than essentially efficacy and that sort of data.

That may be very important because I would imagine if you had to patient who was particularly allergic to one drug, then that valve shouldn't be considered or prosthetic device, whatever it might be.

DR. CURTIS: Yes, I agree.

DR. SETHI: I think that we should put everything in the labeling, whatever we want to put in there. I think that is really a very important topic. You know, we put so much attention to labeling. You know, we should do this. We should put a warning there and contraindications here. And when you ask your colleagues, you know, did you read that labeling, nine out of ten tell me that they have not read it.

So, the question is how can we enforce the reading part of it. Do you have any suggestions on that? If the detail man comes to me and tells me, you know, it is good, I will not go and try to read the label there to make sure

that he has told me the right thing. So, I think this could be a false sense of security that we are putting the silver in the labeling.

I don't know how to make it better, but it is something which is part of life.

DR. CURTIS: It took a whole lot less time to go through those 25 questions than I was anticipating. So, I think we have a little extra time. If anyone on the panel wants to make any comments or any issues that they have thought about since this morning that they didn't have a chance to bring up?

DR. FERGUSON: I would like to get some feedback since I am so confused. I would like to get some feedback from Tom and Don and others. I mean, has this been a help, the exercise that we have been through today?

DR. CALLAHAN: Yes, certainly we have learned some things. But one of the issues I would like to go back to is that we left it just before we left for lunch. We said, well, maybe there ought to be a demarcation between the antibiotics and the sort of silver diazines that we looked at before. We started to toy around a little bit with what kind of clinical studies and we sort of ended -- I don't know that we ended up with any conclusions, but we sort of said, well -- I think Dr. Danner said, well, maybe there would be a clinical trial required and maybe the P value

would be less and we wouldn't be -- but I don't think that issue ever got resolved. I know there were folks who said, well, I am not sure that is required.

So, I would like to push that issue a little bit more if I could. I mean, basically we are going to be putting these in -- we have heard some discussions, quite a bit of discussions about antibiotics you wouldn't want to put in and we heard discussions about some of the risks and some of these questions sort of addressed the methodology of how we go about assessing it, but if we are saying that -- are we saying the bar should be higher or lower or the same? I am not sure we have got a clear discussion on that.

DR. TRACY: I think the point that is important is that the mechanical valves are different from the bioprosthetic valves. So, I think that the issues dealing with evaluation of them is going to be a little bit different from the mechanical valve.

My feeling is that to statistically prove efficacy in terms of reduction in infection is possibly impossible from a logistic standpoint and it is better studied on the long term ongoing postmarket surveillance, which would have to be enforced. And that probably it would be reasonable to expect some level of proof that early on you are not getting an enormous increase in infection, but I wonder before we can even answer that if we could learn more from the animal

model, if we could find out what organisms really do infect sheep and learn something more from that that might reassure us that we don't have to have -- you know, give us a better guidance as to how many patients we would actually have to have involved in a clinical study.

But I think my tendency is to go on lesser numbers rather than requiring greater numbers because I just think that the greater numbers are going to be impossible to obtain with any kind of time feasibility, economic feasibility.

DR. HOPKINS: I can reiterate a little bit what I said earlier but the -- all four sort of subgroups, if you look at it, the mechanical valves, which would also include things like pacemaker leads and pacemakers, the sort of all hardware stuff that is impregnated with an antiseptic, the bar is relatively low and then I think you have to show safety and ultimately you are going to show efficacy in whatever animal studies you can, but ultimately and probably a prolonged postmarket type of follow-up study, where it is a surveillance or a required or a conditional approval, et cetera. You are going to have to in probably all four categories do a postmarket surveillance type study to get sufficient numbers.

When you move to the level of biologicals that are impregnated with an antiseptic that has the potential effect

on durability, you are going to have to do, I think, some animal models to show that you can extrapolate the benefit from the mechanicals to the biologicals and then you are absolutely mandated, I think, to do survival studies, survival of the valve, as well as the patient, for a fairly long period of time because the knee and durability occurs somewhere between 7 and 14 years, depending on the valve.

So, that is committing the industry, if you will, to a pretty prolonged follow-up to prove that you haven't deteriorated the durability of the biological valves by adding this treatment to the skirts. I think that becomes even more important on the stentless type of valves where the actual distance between the compound and the biological component of the valve may be very, very close.

When you get to antibacterials or antibiotics, I think that the bar is raised higher. I think you are going to have to show some efficacy in preclinical trials. You are going to have to do something like a Phase 3 trial of some form to show that there is not a disaster being created in those patients. You are going to get buy in by the infectious disease community on which antimicrobials should be incorporated, answering all those questions that we talked about and then once again a prolonged ten year, seven year type of follow-up that would tease out the efficacy issue. So that at least ultimately we knew whether it was

efficacious.

DR. TRACY: Any study that would be done, though, I think it would be important that it would not mandate a controlled population. You have controls. You have historic controls. I don't think it would be reasonable to regardless of the size of the study to expect a controlled population.

DR. HOPKINS: No, I am not proposing a randomized prospective trial. Something above a registry but short of a prospective trial, some follow-up and it wouldn't have to be all hundred thousand valves implanted every year. I mean, there is a subset that could be identified that over the course of five years or seven years would begin to give you the answers.

DR. CURTIS: I am not sure I personally buy that the issue of biologicals is so much more worrisome than using antiseptic coatings or whatever there. We have to raise the bar as high as some of the other members of the panel are saying, but I think that is the general consensus that the rest of -- many of the rest of you feel that that should be raised higher. So, I would have to defer to that.

I am not sure myself if I had to put my nickel down on it that I see that the risks are so different with what we are talking about with some antibiotics in the valves that I would approach them all that differently than

I would from any other change in the valve myself.

DR. FERGUSON: I want to raise another issue if I can, just to bring it back in to the loop, and that is the issue of the vascular grafts. In point of fact, if antibiotic coating, if you will, is used in products, it is going to be used to a much greater degree in vascular grafts than it is in valves. We have been talking about valves all day. But in point of fact, that is where the action is going to be and I don't think we frankly have addressed a lot of the problems with vascular grafts in terms of -- we have been talking about a little bit of antibiotic on a little piece of cloth is, again, to me much different and I think the problems are going to be much greater to sort out the situations when you have got large grafts that have to be completely impregnated because they are cut.

I don't think what Jeff said would be apropos for this because they always tailored and trimmed. So, they would have to be impregnated from top to bottom. They do not endothelialize or get covered with pannus sometimes forever. There is raw surface there.

So, I mean, there are a lot of other issues, I think, that in the vascular field that we don't have -- I hope I am not hurting anybody's feelings, but we don't have any real vascular people here to help us out with that aspect.

DR. GILLIAM: I just wanted to agree with Anne about one thing. I am not -- I think early on we decided that the mechanical and the bioprostheses were different and, indeed, they may very well be, but I think if the -- it may be possible to obtain in the preclinical stage data that shows a particular antiseptic, antibiotic or whatever stuff we end up putting in these leads is not at all an injury to the leaflets and we may find that that would be perfectly acceptable, to treat it much like we would treat the mechanical valve in that instance.

DR. CURTIS: Thank you.

I don't want to get away from the vascular graft issue because it is true we didn't talk about that very much. I think we should just summarize what could be the potential differences or issues related to vascular grafts.

One of them is that since you are talking about a larger surface area and, therefore, larger surface area coated, I suppose there could be a potential for higher drug levels. You could have higher certainly detectible levels in the blood.

How would that be an issue? How different is that in terms of what we are looking at? More risk of resistant organisms? Greater duration of activity because of the fact that they don't endothelialize and whereas in a heart valve you might expect that to happen relatively early. Maybe in

vascular grafts you want it to be designed so that the drug reaches out and ends its effect within a certain period of time.

On the other hand, maybe there is an advantage to having certain antibiotics reach out over a long period of time, although the resistant organism issue is very real.

Anybody want to make any comments on those points?

DR. RELLER: Although the dynamics between these two devices and the indications, et cetera, are different, to me the fundamental issues are the same. There are in my mind sufficient questions that have been expressed by others, having to do with durability, safety and in some ways even more so with the vascular grafts, having to do with the antibiotic issues that before clearance, studies demonstrating safety would be necessary.

Something else that multiple people, including Dr. Hopkins, pointed out quite early in the day that -- and Dr. Domanski -- maybe by just being absolutely clear on the labeling of what these do or don't, what the data show or not, maybe skirting the fundamental issue, because one has to juxtapose skirting the fundamental question, coupled with the comments made that if these don't prevent infection, why bother? What use is it to incorporate antibiotics if they don't reduce infection.

There are a lot of pitfalls in those 20 questions

in terms of gathering the data that would help one to develop a device that potentially could reduce infection, but at the end of the day, it seems to me without a study or studies that demonstrate, including the things that could be done in the animal model that would warrant the added expense of going into clinical trials, at the end of the day, there are sufficient questions about safety and no point in doing it without efficacy, that to me end up with having to demonstrate both of those before clearance of these valves for use in patients.

To me, the only remaining question is what sort of studies would be necessary to give some reasonable level of confidence that efficacy was present.

DR. DOMANSKI: Well, let me ask you a question. What sort of studies do you think would be necessary because I hear -- you know, we are kind of all sort of low key about this in terms of controlled trials and all that kind of stuff. I mean, what are you suggesting?

DR. RELLER: What I would like to see is what you like, a big one.

DR. DOMANSKI: You know, that is a very different point of view from the ID folks you brought in here. Now, I am talking to the FDA. I mean, that is a diametrically opposed viewpoint to most of what you have heard today. So, it should -- I mean, nobody -- you know, the people who are

experts in this field are calling for something completely different than what the rest of this panel is used to or intended to, I guess. That is important. I mean, that is an important difference.

I can't adjudicate it. I am not smart enough, I don't think, but I am concerned that people who really are experts in this particular area are more concerned than we are. I am not sure they are more concerned than I am. I am getting more and more worried.

DR. CALLAHAN: That is what I wanted to delve into a little bit more. There is, obviously, a dichotomy between the groups and the infectious disease people are really saying, well, if it is anti-infective, prove it and are laying out some risks that they are thinking. One of the -- we can try to assess how great those risks are, I guess, but there is clearly a difference. Maybe that would be worthwhile just trying to pursue -- but then you have to get into organism by organism and saying, well, how great is the risk here versus there, but earlier Mike was asking the question is this really a catastrophic Pearl Harbor that we are looking for and can the infectious disease folks say -- you know, give us some feeling as to how we might know that?

Certainly, you have given us examples as to which ones to stay away from, but those are mainly from a use of antibiotics for other reasons. So that the other

antibiotics will be -- still remain as beneficial. In terms of the -- I don't know that -- can we get without talking about specifics into some of the likelihoods? What is the probability that one of these will --

DR. RELLER: Part of the rationale that I am attempting to put forth is there has long been a concept prevalent that antibiotics, they might not help, but they won't hurt anything. Let's just give them. I think we are living in part with the consequences of that. There are serious infections with vancomycin resistant enterococci, for example. The specter of staphylococci that are not as susceptible among the coagulase negative to vancomycin as they once were.

Fortunately, though, there is an intensified effort, a resetting of break points at the last meeting of the NCCLS, the National Committee for Clinical Laboratory Standards, because people are concerned. It has happened with enterococci. It has happened in pneumococci and everyone expects it to happen -- it is just a matter of when and adjusting the standards to be able to pick up resistance of staphylococci to vancomycin.

So that when I look at those issues and what bothers me the most is the concept, well, it is not going to hurt anything. So, let's just -- and then you have got all of this wide repertoire of devices that might logically

incorporate antimicrobials from catheters to grafting material to different kinds of valves. Let's just do it and see what happens and, you know, watch postmarketing.

When one looks at the relatively small risk of infection with excellent surgical technique and currently available valves, the risk is actually very low, admittedly, very difficult and especially when it is with resistant organisms, difficult to take care of.

So, it seems to me in embarking on a big unknown, it would be very wise to say, as Dr. Alpert has pointed out, where should a line -- this is where we draw the line, that if you incorporate antibiotics, the sole reason for which should be to reduce infection, that we want to see evidence that it does that and as part of the postmarketing surveillance of every infection that occurs, after putting in these antibiotic impregnated valves, that one is not encouraging or promoting or selecting for organisms that are more difficult to treat than what we already have to deal with for those relatively few patients, who develop infection after placement of artificial valves.

DR. CURTIS: So, if you are really saying that a study would need to be done involving several thousand patients to prove a lower risk of infection before marketing the device, if that is what your conclusion is, I don't think it is feasible. I really don't.

DR. RELLER: What I am saying, before the -- whether or not anyone reads it, I mean, what this is -- an enormous amount of effort is put into accuracy in describing performance of a product having to do with safety and efficacy, that I think at a minimum, you know, a new valve or a valve with antibiotic should perform as well as, you know, a valve that is out there now, the OPC criteria.

To put efficacy into the label, I think one needs more than that and you have to have studies that show efficacy. Now, one could get around the issue by simply saying comparable performance, nobody is claiming efficacy, but I like Dr. Domanski's, you know, statement earlier. Come on, who are we kidding.

I mean, these things, their only reason for being is to prevent infection and if they are going to do that, then avoiding saying that they do it in the label to enable them to get on to the market, I don't think we have accomplished anything.

DR. DOMANSKI: I may have a formula for peace in our time here.

DR. CURTIS: Please, go ahead.

DR. DOMANSKI: You know, I think that it sounds to me like the thing that I would worry about in doing this -- I mean, we are shooting a lot of prophylactic antibiotics. I mean, if the concern is the general development of

vancomycin resistant strains, the heart valve is such a small part of that, that I wonder if that is where I would focus huge amounts of effort, time, money and so forth to hold it off.

If on the other hand, the concern is that in a given patient -- and I do hear this concern -- please, correct me if I am wrong -- I hear the concern that in a given patient with a variety of bacteria floating around, that you are going to select the bad ones that are resistant to the antibiotics you have. Then, in fact, one should see that in the postmarket surveillance. One would not expect that to be a catastrophic problem. One would expect to see that as a 1 percent difference ten years from now. And I wonder if one should hold or make massively costly studies to find that 1 percent of these people who get valves.

You know, it starts to be -- begin to wonder where the research dollars ought to go and I just -- and they are dollars whether they are industrially generated. You know, they are coming out of the -- you know, it is sort of -- in the grand scheme of things, it is a zero sum game. You know, in the end the patients and all of us pay for it.

I think maybe the postmarketing thing, if that is the major concern, is where it ought to go. I mean, gee whiz, we are SVE prophylaxing a billion people with absolutely no evidence -- a billion is, obviously,

overstating, but we are massively prophylaxing people, doing SVE prophylaxis, which would have the same community effect.

I think we are probably safe in doing that and I think in the larger scheme of things the expert -- I think the expert input is exactly right, that maybe that is a reasonable theoretical concern, but I think the place where we ought to try to pick it up is not in a randomized controlled trial of mass numbers of people, but rather in the postmarketing surveillance because I think the down side risk is not great enough to justify that.

DR. CURTIS: I agree.

DR. FERGUSON: I would submit that looking at it as only a randomized controlled trial would give you the answer is totally ignoring the -- not only the results of experimental studies but the possibility that these studies can be done under controlled conditions that you will never achieve in the field in humans.

I understand it is an animal model study, but that is after all the way the heart valve, if you want to use that as an example, got started to begin with and, of course, we had to prove it in humans but it seems to me like that you can design experimental studies with all of the expertise that we have, that Rick has demonstrated already, told us about -- you could design studies where you can introduce the bacteria you want to introduce and you can

introduce it in a way that you can check whether the tip is being -- the coating is being effective and so on. I mean, there are lots of animal studies that need to be done before we go to the randomized trial or even talk about it, to me.

DR. DOMANSKI: But I am not sure I would keep the things off the market for huge amounts of time.

DR. FERGUSON: No, I agree with that, too.

DR. DOMANSKI: I think this one, I think it answers my question. The thing that I was worried about and, Bob, maybe you should weigh in if you think what I am saying is wrong, but I just don't see the Pearl Harbor. What I see is a difference of a percent or two somewhere. That would be a big deal and we would take them off the market down the pike, but I don't see some catastrophic development of major problems.

DR. SIMMONS: You know, I guess, you know, hearing you talk, you know -- I am not an expert in the area -- but it seems like this is the time to draw the line in the sand and say, you know, we have been wishy-washy about these indications. We have struggled with this thing yesterday. The only reason this thing is on the device is to prevent infection and it either should prevent infection or it shouldn't. This is the time to say this is a drug delivery device. You have to come up to a higher standard than a mechanical device.

So, let's say it right now. It is a drug delivery system. Prove the drug delivery system works or it is not even worth having.

DR. CURTIS: But in what way?

DR. SIMMONS: So, let's draw it right now. I think a postmarketing -- you know, I think you still have to do a premarket analysis, just to assure me. And maybe it doesn't have to be a thousand patients, but you have got to at least come up to that 800 patient years or something or maybe 300 patient years, some number like you mentioned before, 200 patients followed for two years or something, to get it on the market, but only approved with the condition that five years from now, you know, this panel sits down again, reviews the literature and decides does it get to stay on the market or not. And you have to have 5,000 patients or 10,000 patients followed for however many years it is going to be on --

DR. CURTIS: Because, I think, ultimately -- you know, I think that is what we are saying, if you don't ultimately prove it prevents infection, there isn't any reason for it to be around.

DR. DOMANSKI: But the ultimately is clearly the operative word. Otherwise, we just don't get any new devices. That is a countervailing problem is that you make it difficult to produce any improvement and pretty soon you

are just stuck with whatever you have got. So, there is a countervailing argument to let it be on the market.

DR. TRACY: But I think it is different. I very much believe we should have postmarket surveillance. I think that is a very different level of burden on the industry and that may make the -- to me, I think it is. Maybe I am completely wrong about this, but it probably means the difference between the device happening or not happening, would be my bet.

I also think that it is going to be more feasible to do -- to get the answer by watching more patients over a longer period of time than with a study that is going to always be trying to keep it to the minimal numbers premarketing. So, I think the likelihood of answering the question of whether this thing really is effective is greater -- the chances of answering that question with a postmarket surveillance. I don't know if that is a feasibility to say in five years you come back and if you can't prove it, then we pull you off the market. I don't know if that is --

DR. DOMANSKI: We also haven't seen individual patients that we have SVE prophylaxed, in effect, super infection with resistant organisms. I understand that the widespread use of antibiotics in the community is a different issue and it means the development of resistant

organisms, but since our quantitative use is very small relative to that, I am not worried about the community thing. And we haven't seen it in the other model, in fairness.

I mean, I understand the theoretical concern, but in the one model we have got, which is SVE prophylaxis, haven't seen it. We don't see those people developing odd resistant infections after their dental procedure.

Does that make sense or doesn't it? I mean, tell me if I am wrong.

DR. DURACK: Can I make a point?

DR. CURTIS: Sure. Come on up.

DR. DURACK: This question of efficacy seems to have become so central that it might be worth just recapping a little bit on this SVE prophylaxis analogy because it is an analogy that we have been looking at for a long time.

If we go back to the fifties, in the 1950s we got into the habit of giving systemic antibiotics for preventing streptococci from sticking on heart valves. Twenty years, nobody knew if it worked. In the 1970s, the animal model came along and it was possible to say with absolute certainty, antibiotics stop some infections when they are given in the right way under the right circumstances.

There is no question about it. It was proven. Now we are 20 years later again. We are no closer to

proving efficacy in the human being actually. We only have proof in the animal. We don't think we have done a lot of harm in the human being. So, this doesn't give the answer, but it gives a kind of an analogy or a model that goes a little towards what you are saying.

The animal model probably is important. It can provide proof in a warm blooded mammal that something is happening. After that, you will have to wrestle with the question of the postmarketing study and whether it is really doing any good. It is possible that you could get the proof of efficacy in the animal model and then go 20 years and not know whether you were doing anything useful in the human or not.

DR. DOMANSKI: Yes, it is just that you would have gross things. I mean, if it turns out that this theoretical concern is more than we are thinking, we are going to see a percentage increase that is substantial compared to historical controls.

DR. TRACY: And also some degree of study ahead -- nobody is saying just put these things in right tomorrow. I mean, there has got to be some --

DR. GILLIAM: But at the same time if we had the device and, let's say, for instance, we had a device that was attached to a valve that delivered a certain amount of antibiotic and after five years we compared that with the

infection rates of the ones without the drug and they were exactly the same, but then we looked at the complications of everything and they were exactly the same. In short, the drug did exactly nothing, which might happen.

At that point in time, you know, I don't feel compelled, you know, that it should be taken from the market. In effect, essentially it is a step in the production of this device that the company is doing and is doing nothing to enhance their product. I think it would be more likely at that time the company would look and say, well, gosh, why do I go through the expense of doing this, you know, because the market forces would probably bring that back in line.

I don't think that I would worry as a body here that demand efficacy unless they claimed some response in that statement because, you know, without doing the clinical study, the randomized study really to show that this antibiotic works, I think without that, they should not be allowed to even make a claim.

If we can on the other hand later on show that it does no good, I think then we should definitely be able to publicize that this doesn't do any good.

DR. CURTIS: Well, of course, the problem we run into is that, you know, if you release it you say it doesn't make a claim but here it is. It is an antibiotic in there.

We all assume it is better than not having it or what the heck, maybe it won't hurt --

DR. DOMANSKI: You know, if all else fails in the labeling, you could just say what you really mean and that is that it stands to reason that this may work. It is in for that reason, but it is not demonstrated in human trials. I mean, you could just actually say it.

DR. GILLIAM: Well, I think we have to say that.

DR. DOMANSKI: Some people actually do --

DR. GILLIAM: But I think that it might very well be that it does work and this may turn out to be --

DR. DOMANSKI: Well, not yet demonstrated. I am sorry --

DR. GILLIAM: Well, I think that we should label it that we don't know. It has not been demonstrated and it may have no effect at all, but I think that if we do -- I am in favor of a postmarket, you know, very closely watched study. I don't think I could see anything that could be done premarket that would give the numbers that would make me comfortable, that you have done anything but waste time and a lot of money and still not have the answer, if you will.

DR. CURTIS: I guess the question is how well would that study be done and how would we get the answers because I guess what I was trying to get at is for a company

it may be that simply getting the device approved by the FDA and marketed would be good enough. They are not maybe potentially interested in whether or not they get proof of efficacy and get that on the label because simply having a heart valve they can go out and sell that has an antibiotic in it, they don't have to say it is on the FDA label, but people will kind of think it is a good thing.

So, in which case then, do the postmarketing studies get done well to get the answers we want?

DR. GILLIAM: Well, they may not done, but I would ask now how is that we know the occurrence of bacterial endocarditis now? I don't think that was a precondition of a valve being out there. I think that that information is going to be obtained.

DR. DOMANSKI: There actually, though, has been a historical decrease in the rate of infection with the use of prophylactic antibiotics in surgery and while it is not supported by a randomized trial, which hasn't been done, the data really are pretty compelling. I mean, I would feel very uncomfortable going backwards with respect to that. And if you saw the same sort of thing here, I think it would be similarly compelling or similarly non-compelling if you didn't see it, I suppose.

DR. HOPKINS: Studies have been done for other reasons that give us that data. The questions have come up

as to whether biological valves are more resistant than mechanical valves and study after study after study over the last 20 years has been done on that very question. And putting all those together in a sort of a meta-analysis type of way gives us those incidences. I am very comfortable with historical controls for such a study because we really have a lot of data on prosthetic valve endocarditis.

But there is no point in mandating a postmarket study if you are not going to act on it. So, unless at some point we as a panel or some other mechanism reviews this data at three years, five years, seven years and ten years, with some thought of doing something about it, then let's not waste the money or our time.

DR. GILLIAM: I do think we need to review it but I think there are several outcomes when we review it. We could, one, demonstrate a very positive effect; in which case, we would all be very comfortable with continuing the drugs manufactured as it was. If we go five years, it may turn out that the only valves that are manufactured all have this drug in it and that it has no effect; in which case, we may say, well, you don't need to put it in. It is not doing anything but it may be in there anyway.

DR. HOPKINS: In the antibiotic case, I think the theoretical construct is it is going to affect the early phase SVE anyway.

DR. GILLIAM: So, we will know the answer pretty quickly.

DR. HOPKINS: So, you probably should know in the disinfectant or antiseptic concept, that is going to take a little longer to understand whether that has an effect on the early and the late phase. But I think you would have at the end of three to five years in a post-implant surveillance study, well designed, picking maybe ten centers that has good follow-up, I think you would have your answer.

DR. GILLIAM: And if the answer happens to be bad, of course, it makes it real easy to alert the -- to remove that particular drug from the market.

DR. DAROUICHE: Can I share a single slide with you?

DR. CURTIS: Sure.

DR. DAROUICHE: I have to say that I truly agree that the main difference between antibiotic and antiseptic coating of cardiovascular implants is the fact that with antibiotic coatings there is always the potential concerns for the development of antibiotic resistance. As we have agreed with our infectious disease experts that, in fact, antibiotic resistance does pose a public health hazard, there is a potential concern that, in fact, there is an increased usage of antibiotics systemically, which we know is the major culprit for developing antibiotic resistance,

that ultimately results in emergence of antibiotic resistant organisms outside into the community.

With antibiotic coated vascular devices, however, that is not what we have seen with central venous catheters because as I have said this is not a drug delivery system. We get no systemic blood level and even if the patient has a problem with an infection of an antibiotic coated vascular device, that patient can still be treated with vancomycin, which has a different mechanism of action than either of the antibiotic agents listed and, therefore, should have no negative impact, neither on the patient nor on the community.

Now, having said that, it becomes apparent that, in fact, there is no reason to have double standards in approving an antiseptic coated versus an antibiotic coated vascular device with regards to efficacy because what I have heard a few minutes ago is somebody has mentioned that, well, the antiseptic coated device was approved without any need for clinical trials showing efficacy. But if we want to coat with antibiotics, if anything, we have to prove clinically that these devices are efficacious before we release them into the market.

Now, we all know that surgeons are very smart, actually they are smarter than internists, and they know that if we reduce colonization, there is a good chance they

may reduce likelihood of device-related infection. So, when it comes to safety issue, in fact, this double standard does not stand. If anything, it should be the opposite.

These are the results of a clinical prospective randomized study that we just finished. This is a study that was done in a total of 13 hospitals and we compared the outcomes of antibiotic coated catheters versus antiseptic coated catheters and guess which one was more efficacious. It is the same one that somebody is proposing that we prove is efficacious before we release it in the market, while, in fact, we already have a precedent for an approved antiseptic device that has not proven to be beneficial in patients; yet, it is approved.

Antibiotic coated devices were actuated with a threefold lower rate of colonization than antiseptic coated devices. More importantly, catheter-related blood stream infection, the only important clinical outcome, was twelvefold less likely in association with antibiotic versus antiseptic coated devices. I am not saying that antiseptic coated devices are not clinically beneficial. In fact, they are when compared to uncoated.

But antibiotic coated are expected to be far more efficacious. So, please, when you try to put double standards, I really urge you to please read the literature and keep this in mind.

Thank you.

DR. RELLER: Where is this study published?

DR. DAROUICHE: -- in The New England Journal of Medicine.

DR. RELLER: I think it makes it very difficult without seeing the methods. The diagnosis of -- and the cardinal difference that you pointed out is blood stream infections and with what organisms, the criteria for definition. I mean, I just think that without published data and undergoing review, I am unwilling to simply roll over and say the answer is on the slide.

DR. DAROUICHE: I am really not asking you to roll over.

DR. RELLER: The devil is in the details.

DR. DAROUICHE: I am asking you to please keep this in mind when you consider one device versus another. These are the same definitions that the CDC established. These are the same guidelines that have been used not only in the study but in all of the antiseptic and antibiotic coated central venous catheter studies that have been done so far. We followed exactly the same protocol and we had the same definitions.

DR. RELLER: I don't want to belabor this point but the CDC definitions for blood stream infections -- and they know it -- are seriously flawed. Included among them

are the isolation of a single blood culture with coagulase negative staphylococcus and intent to treat. That is not establishment of blood stream infection.

DR. DAROUICHE: In fact, I am sorry. In fact, I disagree with you. These are not the definitions of the CDC. The CDC defines the following: The catheter -- and Dr. Durack can assist me with this -- an episode of catheter-related blood stream infection is defined by the growth of the same organism from the catheter and the blood stream in a patient who has clinical manifestations of sepsis and in whom no other etiology for the bacteremia exists. These are the definitions posed by the CDC.

DR. RELLER: Let's see what the peer review of this paper shows. There is more to it than what we have been presented.

DR. DANNER: Actually, could I get back to the main issue here.

Mike, why can't we do a study showing efficacy? Why is this so horrible, prohibitive, incredibly expensive, can't be done? Let's just throw up our hands, let somebody produce a marketed device, sell it, make profit on it and not know if it has any effect at all? Why is it so prohibitive?

DR. DOMANSKI: Yes, I know, and, in fact, I have long been a part of this panel, both as a regular member and

so forth and one of the things I have pushed over the years is controlled trials. But I think that you have to -- that the numbers would probably be very large.

DR. DANNER: How large?

DR. DOMANSKI: They threw some numbers up earlier.

DR. DANNER: They didn't look that big to me. I mean, in other words if you assumed --

DR. DOMANSKI: What numbers did they put up, Bob, because maybe I was looking at the wrong line or something.

DR. DAROUICHE: Yes, I am sorry. This clinical trial was done with the objective of showing whether significant differences in catheter colonization --

DR. DANNER: Yes. I am not interested in catheter colonization, though.

DR. DOMANSKI: Let's see the slide again and look at the numbers because maybe I just read the numbers wrong, too.

DR. NAFTEL: I am still David Naftal. I still know who I am.

I have got the sheet in front of me. To go from 1.2 percent in one group in a year down to 6 percent in another group. That was the really bad one and that was 4,000 in each group. So, that was a thousand in --

DR. DANNER: Could you show the slide again? I would like to see the slide.

DR. NAFTEL: As I said before, it is a bit of a numbers game but see this is assuming 1.2 percent in one group during the first year; .6 percent in the other group. So, it is the second line from the top.

DR. DOMANSKI: Yes. You see, Bob, and that is so -- you have to double that. So, you are asking to recruit 8,200 patients in order to put some antibiotic into their catheter in patients who are already having the things dipped, you know, and having antibiotic shot and so forth.

DR. DANNER: And you feel the efficacy would only be 50 percent?

DR. NAFTEL: That is a guess. I mean, the dipping stuff showed 80 to a hundred percent efficacy in the data we saw before.

DR. DANNER: But these are in addition to that. So, you have to -- it is not quite the same thing to say that, you know, you are starting from the same spot because you are not. You are starting from a spot where there has been a lot of attempt to sterilize it.

I don't know what the numbers would be. Obviously, if you are willing -- if you think it is 1.2 to .2, then, of course, the thing becomes -- you know, it becomes more tractable. It is not a small study as these industrial studies go.

I think that I would guess just -- you know, one

of the things that is happening in clinical trials and I think it is almost a general statement is that all the placebo group numbers are going down. That is, you expect, based on historical controls for congestive heart failure to have a certain mortality in a certain group and we are finding that that is not the case, that it is lower.

I wouldn't be surprised that if you did this study and you are a non-catheter group, that you wouldn't see in your control group, you know, if you will, less than 1.2. I mean, I think 1.2 to .6 probably is asking a lot of this thing. I think it may be lower.

DR. DOMANSKI: Depending on how you picked your centers, you could also get a higher infection rate, right? I mean, isn't that how this works.

DR. TRACY: Well, I think another thing --

DR. DOMANSKI: Well, he is talking about doing a randomized trial. It is a reasonable question. You see, I want to make sure that I am not saying something wrong. I am taking Bob seriously. It is not an argument at all. But the concern that I have is even if you ask for an effect -- I don't know if you want to call it a 50 percent drop or a hundred percent drop, but you are asking them to do an 8,000 patient trial.

DR. DANNER: What if you take the line from the bottom and say that you are going to go from 1.2 to --

DR. DOMANSKI: I think you are asking --

DR. DANNER: Is a 4,000 person study too large for this area?

DR. DOMANSKI: I think that that is --

DR. DANNER: I think it is rather a large study, but I think even more than that, I think a clinically significant effect is what you are asking them to demonstrate and I think you could miss a clinically significant effect because your study would be underpowered. I would be a little nervous about asking the thing to go from 1.2 to .2 or to .4.

DR. TRACY: Yes, because if you did that and you only had a thousand patients in each group and you had, you know, 1.2 percent in one group and 1 percent in the -- you would get an n that -- a P value that wasn't significant and then you would say, oh, it doesn't work and that is just because you are underpowered.

I think if you reduce the infection rate in half, that would be clinically significant.

DR. DANNER: That is a pretty significant difference and it is a pretty big group.

DR. TRACY: Well, just one other thing you have to remember, too, with this whole issue about clinical trials is when you are factoring in how expensive it is, how worth it is to do the trial, you have to look at your eventual

market, too. I mean, it is -- you know, it winds up being cost issues, but it is a very, very different thing to say if you prove a systemic antibiotic works, it is going to be used in millions of patients a year versus, you know, the entire heart valve market is a hundred thousand patients a year and, you know, that has to be factored in when you are designing these.

DR. DOMANSKI: This whole heart valve thing is a real problem because they really work pretty well in things. We went through this, not just talking about infections, but talking about better heart valves and one of the difficulties is that if you have to do trials this big, it is pretty hard to ever bring a somewhat better valve onto the market.

I think the interesting thing is from a practical point we are starting to reach the limits of what you can do with these clinical trials, what is reasonable to do.

DR. DANNER: What about studying a different device, studying AV fistulas and renal transplants or kidney failure patients or something like that?

PARTICIPANT: It is a different device.

DR. DANNER: Yes, somebody said it is a different device but some of the principles are the same and I think that is an interesting thought. I mean, it might be more reasonable to do it in those --

DR. TRACY: It might be, but at this point I don't think we know the rates of infections, the types of organisms, the other issues. You are dealing with people who are on renal transplant who already are receiving antibiotics for a variety of --

DR. DOMANSKI: I mean, renal failure. I misspoke. Renal failure patients with AV fistulas. There are a lot of those patients and they get infected a lot.

I think it would be an interested study because if the silly thing came up positive it would be not precisely analogous but it would be pretty compelling evidence that that sort of thing would be useful.

DR. DANNER: But you have a problem in that you have a low incidence of the disease that you are trying to direct things at and there is maybe not a -- because of that low incidence, the number of patients actually benefiting from this antibiotic impregnation is tiny.

Though I agree that the risks are small, everything is small and it is possible that, you know, you could be trading problems with infection to problems with allergic reactions. I mean, you had mentioned the known incidences of allergic reactions with antibiotics and, hopefully, with these devices, it won't be anything near what is published on antibiotics. Hopefully, with the much lower amounts and the amount leaching out, it will be much

lower because I think what is -- the allergic reaction rate with antibiotics is unacceptably high.

DR. DOMANSKI: But, Bob, haven't you already bought that because these people all get prophylactic antibiotics anyway. I mean, haven't you already bought the allergy risk.

DR. DANNER: Well, now you are giving different antibiotics. So, it is not the same antibiotics. So, you are increasing or compounding that, plus you are having devices in that may have antibiotics associated with them for a very long period of time.

DR. DOMANSKI: Is it really not the same antibiotics? I mean, I haven't heard anybody say exactly what antibiotics they are going to use, but is it really different ones?

DR. DANNER: Well, presumably we are not going to use vancomycin in the cloth, right?

DR. DOMANSKI: Yes, but --

DR. DANNER: A lot of people don't use vancomycin apparently with their surgery.

DR. DOMANSKI: No, but they will use saphaszolin(?) or something like that and saphaszolin is also not going to go in the cloth. So, it is a whole different set and probably multiple -- because we are combining.

DR. RELLER: Would it -- you know, if it is not substantial or any improvement over what is currently available, one wonders why bother. But if one wanted to try to come to some reasonable ground to enable the possibility for an improvement, could one do a, in round figures, 800 patient year study that would show that this valve or a potential valve that had antibiotic in the ring or however it was incorporated, worked as well and if it were a totally new compound that the valve was made from, a new design worked as well as existing valves for then more widespread use and if a firm had animal data, the sort of studies that Dr. Hopkins outlined earlier, and the FDA in a collaborative way said if you want to go beyond simply marketing this, to marketing it, including in package insert for reduction of infection, now having established that it is reasonably safe or as safe as the other valves as regards how it works in thromboses and so on, the criteria on the OPC list, that then through marketing surveillance, I mean, tracking every valve place to see whether the spectrum infections is different, if there were resistant organisms, et cetera. And then perhaps a review at some time later by the panel, the FDA, would look at the postmarketing surveillance of what happens with these valves as regards infection.

Is the rate substantially lower than 1.2 percent? I mean, is it .6? Is it .8? Is it 2. Coupled with the

animal studies, so that there would be a logical basis for how this worked, that the non-human studies with their 20 questions asked and the postmarketing surveillance on top of a basic comparability study that one could add to the package insert efficacy once it was shown to the satisfaction, with all of these parameters to the FDA and with perhaps advice of an advisory panel. I mean, is that an option?

DR. CURTIS: Actually, I think you are summing up the consensus we have reached. I think that is basically what we all are -- you know, that it would be a reasonable approach.

I would like to ask whether Gary or anybody from industry wants to make any comments about the premarketing studies that were talked about or postmarket surveillance, how burdensome it is, you know. It would have to be several thousand patients here in order to see an effect on infection rates.

The issue came up -- you have been involved in valve studies. How expensive are they?

MR. JARVIS: On a very limited basis. I mean, I think, you know, that industry is not opposed to doing postmarket surveillance. I think we need to keep in mind the cost that we do this and the benefit we receive. I mean, you know, to do 800 valve years, we are talking three

to five years implant time and follow-up. You know the history or lifetime of that valve may be gone if it is a tissue valve. There may be something better along the line.

You know, is it worth it to the industry and on top of that the cost, you know, we are talking several million dollars to do this. We would have a hard time recouping that cost and with the adjunct of more reconstruction surgery being done and on the rise, it could drive valve implants down.

There is a concern. I mean, you know, I don't sit on the executive team of the companies. I would think there would be a decision made at that time is it worth the company's benefit to spend the time and money involved to do this.

DR. DOMANSKI: I think there has to be balance between the public's interest of having things that get on the market that have implied efficacy and safety, that, in fact, has never been demonstrated.

DR. NAFTEL: If I may just say a couple things.

I run an 80 hospital registry of heart transplant data and the one rule in my office is if you call it a registry, you are fired immediately. I despise the word. I know that companies, all of them here, would not -- I think they probably hate the word "surveillance." It would be a real live formal tough study. This would be the real thing.

You don't just kind of look at it and see what happens. It would be a real study and, therefore, expensive.

But it could be done. One thing as we are thinking through this issue, I think we have all said and agreed that endocarditis happens early. After about six or seven months it is all over.

So, the good news would be that a surveillance study could be of short term. It may be five years to accrue the patients or something, but for each patient, at least it would be short term follow-up and that would be something that would argue towards ease.

DR. HOPKINS: I am not so sure that the post -- I would agree with you. We call it a surveillance study or a registry and for want of a better term, but I would agree with you it has to be more formalized than that. But 80 percent of the academic medical centers with cardiac surgical programs maintain the database on their patients linked to the STS database. So, in fact, with some fairly -- I would challenge the cost as being excessive for the follow-up because many of the centers that you would select to do this are already following up all their patients and all you would have to do is add a little bit to that.

So, I am not so sure we are talking about millions and millions and millions of dollars here.

MR. JARVIS: But you are not doing this on an

altruistic basis. You charge us to get that information and in some places that can be fairly expensive to go out and get that data from you.

DR. HOPKINS: On a prospective study, if you already are acquiring at your own cost 95 percent of the data, to get the additional 5 percent of the data that we would perceive for such a study wouldn't be that bad. At the most you would be talking maybe an extra echo. Most of these patients are -- or almost every valve patient anyway gets an echo once a year.

DR. TRACY: Right. I think it depends on -- exactly what you are saying, what you want to include in there. It sounds like what you are talking about is an echo surveillance study, but what I think Dr. Hopkins is saying is right. Most of these people are getting echoes anyway. So, I think very careful thought about what exactly are we talking about in the postmarket -- in surveillance. Is it echo cardiographic evidence for endocarditis? Is it blood cultures? Is it clinical evidence? Is it -- what exactly is it that is being looked for? What is the thing we are trying to prove?

So, I am not sure what study you have been involved in, but the point here is a little bit different here, I think.

DR. HOPKINS: While occult bacterial endocarditis

occurs, most patients who have bacterial endocarditis, who are being followed and captured in a postsurgical registry or database, you are not going to miss the incident. Now, teasing out the specifics of what bug is involved, et cetera, that may be a little more difficult, but getting the gross number that you wanted, which is incidence of postoperative endocarditis, is not going to be a particularly hard or expensive number to get.

DR. NAFTEL: And I would just like to respectfully disagree. I am very familiar with the STS database and really not a good forum to discuss it, but it is a great way to perhaps get the beginning list of patients to now go do a formal follow-up and a study. To my mind, it is nowhere near what you are saying it is.

DR. HOPKINS: No, I would agree that that doesn't replace a formal study. What I am saying is that most centers are already doing this. They have mechanisms in place that you could superimpose. I don't think this is expensive. What we are talking here is that there are members of the panel who are saying, look, before you even get this to market, you have got to do a formal randomized prospective study. You have got other members of the panel saying, look, at the very least you are going to have to fund a follow-up study that over the course of time is going to tell us the answer.

I am saying I don't think it will be that expensive. I don't hear anybody in this panel saying that once safety has been proven that we are just going to turn these things loose and never revisit the issue. So, what I am saying is that what the most compliant members of this panel are recommending to the industry may not be as expensive as you might think.

DR. GILLIAM: I have one question and it goes along with the cost, too. We sort of faced the same thing when we reviewed the indications for implanted cardioverted defibrillators. If, for instance, one company takes a mechanical valve and shows that that mechanical valve is, indeed, safe and let's say they do a major follow-up and they follow 5,000 people and actually show that it is efficacious in lowering the rate of SVE, do we now have a general indication for essentially any company who has a mechanical valve that uses that antibiotic delivery technique which may be there -- I mean, do we -- I mean, is that something we should talk about?

DR. ALPERT: Unfortunately, there are rules about that, but you bring up a very interesting concept and I think what it does is throw a concept to the industry colleagues to consider, based on all of the recommendations made about the kinds of limitations that there would be against -- about choices of anti-infectives, antimicrobials

to be used.

If there were a consensus developed and everyone were to -- that were doing this were to work in the same arena, if you will, of drugs and work together pooling the information, that is one way to get the answer for the clinical community, which is -- and for the patients, which is really important and data that is shared, but that has to be an agreement that the industry makes because currently the statute says that that data belongs to the company who develops the data and we are not allowed to use that information for the approval of products of other companies unless they have right of reference to that information.

So, it takes cooperation across the industry in order to have that information be usable from one company to another or the claim to be extended beyond the individuals who develop the data. There are some models that can be used for the development of that information and placed in a file that we have access to that allows us to share that kind of information, but there are going to be issues about whether they are really comparable, whether the information can, in fact, be applied from one product to another.

But I think you have brought up something that I would suggest the industry be thinking about in terms of planning such trials.

Tom, did you want to --

DR. CALLAHAN: I guess I heard that question a little bit different. I thought maybe you were asking -- certainly if we could get that kind of cooperation, that would be delightful, but I thought you were asking the question if you did -- if a company had a valve and did it once, could they then put it on all their valves. Was that a different question?

DR. GILLIAM: Well, I think it was a combination of both and, you know, what I was getting to was the fact that if, indeed, the company produced a valve. It was out there and -- I understand what you are saying, if the company funds everything, it is their data. They can do with it as they wish, but I guess maybe if we did it a little bit -- if this data isn't done by a company, let's say it is done by a group of universities, then they publish this data -- I may be splitting hairs and I am really -- I just bring it up because I thought it was something that is important to industry, as well as the panel, and FDA to consider now because all we are doing now is talking about some general guidelines and I think that the things that we may get into problems with is it may be that a certain combination of antibiotics may work and another combination may not.

So, if we start planning the study, it may not be one study we are looking at but rather many, many studies of

several thousand people then and I could then see where it can be very cost prohibitive when we start doing a study that uses these two agents in a valve and these two agents in a bioprosthetic valve or this agent plus another agent and so on and so forth. That then becomes, you know, I guess the red flag I would think of is can one company show that two agents worked in a delivery system and then the next company who makes a valve, that this is in the public arena. They publish this data. It is in the general public knowledge. Is that data able to be used by other companies to make the next leap of faith that these two combinations could be used in their valve?

That is what I intended to bring out.

DR. ALPERT: There are concerns regarding publications and their adequacy, as we discussed yesterday, all day. The concerns about being able to get behind that information and how much information you can get behind a published study raise concerns as to whether just publication of a single study would be sufficient for another company to rely on and whether that doesn't put a disincentive in place for people to publish their results. And we are concerned about that as well.

DR. CURTIS: Any other comments?

MR. MORTON: Madame Chair, I will just make a brief one. I realize we have all been at a disadvantage

today because we have talked about several different possible devices, possible antibiotics and I appreciate that.

This morning, I presented a model that, unfortunately, made it very clear I couldn't really talk about a lot of the very important issues, which are the preclinical studies. I will say that with mechanical valves, these are very well characterized. The FDA has worked with us very well to establish a guidance document for the preclinical testing of these.

I think that when we are considering changes like this, we could go forward with a lot of confidence that the preclinical data would show -- would be valid scientific evidence that we would have a safe product.

DR. CURTIS: Tom, did you have any other comments or --

DR. CALLAHAN: Only that you were talking about in sort of a summary, which I guess Dr. Reller sort of did on your behalf, you would end in talking about a postmarket surveillance. We talked about a study with endpoints that you could probably see since endocarditis you can see fairly early. So, you wouldn't have to follow them that long. We never really talked about how big a study, what the n should be or are we talking every patient who got the valve for the first x number of patients and then the rest not?

DR. CURTIS: I think you would have to -- probably a six month study per patient would probably be the most fruitful. It would be better to study more patients for a shorter period of time than a smaller group of patients and try to follow them longer because once you get past the six month point, the risk of infection isn't as high as it is in that initial period.

But I think in order to show the differences in infection rates, you are talking several thousand patients. The calculations could be done, but I think that halving the infection rate would be very clinically worthwhile. So, in order not to miss that, you are going to be talking about some of the n's that were calculated there, maybe 4,000 patients a group; you know, the antibiotic impregnated valve versus the standard valve, that sort of thing and followed out for that length of time.

So, that would be kind of the ball park I would be looking for.

I guess I should just add in passing that I agree, I doubt the STS database would be good enough for this use because I mean how many times have come before a panel here and reviewed a clinical study where centers were enrolling patients and new data was being collected and knew it was for a product that was being studied and there is missing data all over the place. That is when it is a study.

When you are talking about a database and you are getting into -- I mean, a database is only as good as whoever is entering the information into it. And there is always the possibility that you are going to underreport in a database. You are going to have patients who got a heart valve at the university medical center and then get admitted for endocarditis at their local hospital maybe. It doesn't necessarily get reported back to the university medical center.

I doubt very much at our own medical center that we could guarantee a hundred percent follow-up. So, I think rather than just a database, it would have to be a formal study. That is what I would be thinking of, is relatively short term but a large enough number of patients to be able to see that difference in infection rate.

DR. HOPKINS: Dr. Curtis, if I could address that. I agree with you. In our database, we call the patients every six months and all you can tell on that is basically whether they are dead or alive and whether there has been a cardiac event or not. If there has been some event, then it is followed up.

To layer on to -- and that is not particularly expensive to do and we do about 2,000 open hearts a year -- to layer on that a little more formal study -- and I would agree with you, it can be relatively short term, although I

would probably carry it out maybe a year to catch things like pannus -- enhanced pannus formation and that sort of thing. But if you follow the patients at one year with a terminal echo study and there have been no events and the echo is fine, you can pretty much assume that it is an event free interval from the time of surgery to that one year follow-up.

Potentially, you could carry it out even further without the echo. I mean, it would be a cross comparison, but to study even 8,000 patients that way over the course of a two to three study with a terminal shut down at one year, I just -- I can't see that would be terribly expensive and to layer on a level of intensity over what most programs are already doing to follow their outcomes would just be a little added debt.

We have little subgroups in our patients that we are doing studies on all the time. And you are right. The filter gets a little finer when you look at those particular patients and that would happen in the valve picture.

DR. CURTIS: If there were going to be echoes, I would suggest that you would have to have those in a much smaller group of patients. In order to prove there is a difference in infection rate, you need 8,000 patients studied, well, then, so be it. Follow them up for six months or a year and find out whether or not they got

endocarditis and what the bug was.

If you want to know if the valve functions okay, it may sound like, oh, well, they are going to get an echo anyway, but, you know, if it is needed for a clinical trial, we will usually try to get the company to pay for it. You know, you would like that. You get into a lot of hassles about who is going to pay for it and it is an expense to be added.

And I think if the question is does the valve function well, I don't think you need to have 8,000 echoes to know the answer to that. You would probably have --

DR. HOPKINS: I think you are right and you could obtain -- almost all these patients have echoes anyway. You could obtain those reports and then do a sampling frequency or, you know, one in fifty patients or one in a hundred patients.

DR. GILLIAM: You would ask a study that size to be done for every valve with this indication? It would mean that within a company, you know, they would have, you know, multiple valves and I guess I --

DR. HOPKINS: Oh, no, no. I think --

DR. GILLIAM: I could even play, you know, the devil's advocate. What if someone by chance had two valves, put in a double valve, would there be a problem with them getting a double dose of the antibiotic?

DR. HOPKINS: I think you would have to define your parameters to make it a clean study and you probably would talk about a single valve replacement and you would factor out some of the other issues, people who are on steroids, those kinds of things and get rid of that.

But, no, I mean, if you have got five different models of mechanical valves and you show efficacy in one, I am not so sure that it is a great leap to think that there is efficacy in the others. All I am proposing is that safety alone -- I am personally uncomfortable with just showing safety. I would like at some point there to be a response to the efficacy question.

I am on sort of the moderate side of the panel, where I am not so sure that it has to be done before market. I think it can be done after market, but I think it should be done.

DR. CURTIS: Any other issues?

DR. CALLAHAN: I just want to thank you very much, all of you, for a stimulating discussion in the last few days. I am afraid it was fairly intense and all we could promise you is that you wouldn't be bored and I don't think -- I didn't see any boredom on anybody's face.

I don't think the Agency has anymore questions.

DR. CURTIS: All right. Do I have a motion to adjourn.

PARTICIPANT: Move to adjourn.

DR. CURTIS: Second.

PARTICIPANT: Second.

DR. CURTIS: All in favor?

All right. We stand adjourned. Thank you.

[Whereupon, at 3:15 p.m., the meeting was concluded.]